A RANDOMIZED DOUBLE BLINDED STUDY COMPARING THE EFFECT OF ADDING DEXMEDETOMIDINE AND FENTANYL WITH 0.5% HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA FOR ELECTIVE CAESAREAN SECTION

Dissertation submitted to

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

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CERTIFICATE

This is to certify that this dissertation entitled "**A RANDOMIZED DOUBLE BLINDED STUDY COMPARING THE EFFECT OF ADDING DEXMEDETOMIDINE AND FENTANYL WITH 0.5% HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA FOR ELECTIVE CAESAREAN SECTION"** is a bonafide original work of **Dr. BALAJI E** in partial fulfillment of the requirements for M.D Branch -X (Anaesthesiology) Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in APRIL - 2016. The period of study was from JUNE 2014 - JULY 2015.

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DECLARATION

I, **Dr. BALAJI E**, solemnly declare that dissertation titled entitled **"A RANDOMIZED DOUBLE BLINDED STUDY COMPARING THE EFFECT OF ADDING DEXMEDETOMIDINE AND FENTANYL WITH 0.5% HYPERBARIC BUPIVACAINE IN SPINAL ANAESTHESIA FOR ELECTIVE CAESAREAN SECTION"** is a bonafide work done by me at Thanjavur Medical College, Thanjavur during June 2014 to July 2015 under the guidance and supervision of **Prof Dr. R. MUTHUKUMARAN M.D, DA.,** Department of Anaesthesiology, Thanjavur Medical College, and Thanjavur.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University towards partial fulfilment of requirement for the award of **M.D degree (Branch -X) in Anaesthesiology.**

Place: Thanjavur

Date: (**DR. BALAJI E)**

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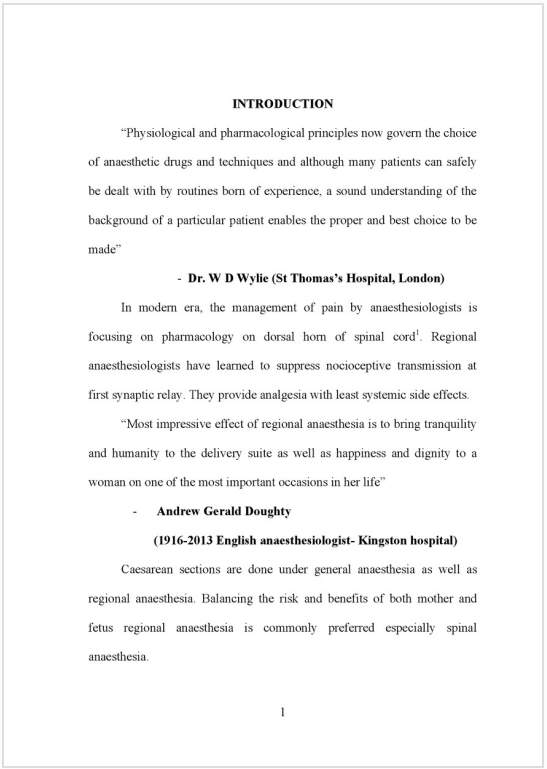

INTRODUCTION

"Physiological and pharmacological principles now govern the choice of anaesthetic drugs and techniques and although many patients can safely be dealt with by routines born of experience, a sound understanding of the background of a particular patient enables the proper and best choice to be made"

- **Dr. W D Wylie (St Thomas's Hospital, London)**

In modern era, the management of pain by anaesthesiologists is focusing on pharmacology on dorsal horn of spinal cord[1]. Regional anaesthesiologists have learned to suppress nocioceptive transmission at first synaptic relay. They provide analgesia with least systemic side effects.

"Most impressive effect of regional anaesthesia is to bring tranquility and humanity to the delivery suite as well as happiness and dignity to a woman on one of the most important occasions in her life"

- **Andrew Gerald Doughty**

(1916-2013 English anaesthesiologist- Kingston hospital)

Caesarean sections are done under general anaesthesia as well as regional anaesthesia. Balancing the risk and benefits of both mother and fetus regional anaesthesia is commonly preferred especially spinal anaesthesia.

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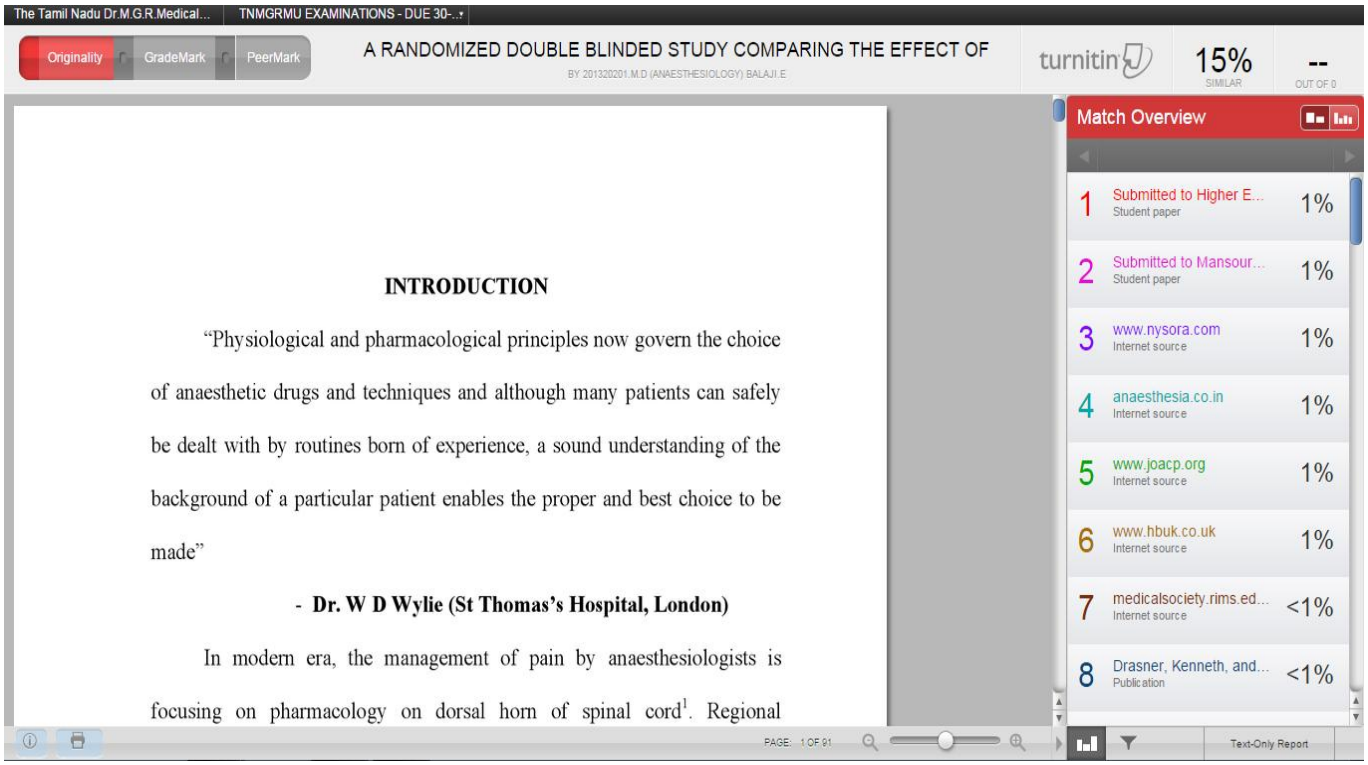
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Caesarean sections are done under general anaesthesia as well as regional anaesthesia. Balancing the risk and benefits of both mother and fetus regional anaesthesia is commonly preferred especially spinal anaesthesia.

The decision to use a particular anaesthetic technique for caesarean section should be individualized based on patients' preference, anaesthesiologist judgment, anaesthetic, surgical, maternal and fetal risk.

Over the years spinal anaesthesia has emerged as the choice for elective caesarean section and general anaesthesia has been reserved for urgent and emergent situations and situations were regional anaesthesia is failed or contraindicated.

Its simplicity to perform and more rapid onset with good sensory as well motor block[2], excellent analgesia and decreased stress response to surgery and intra operative blood loss have made spinal anaesthesia preferable in caesarean section[3].

Most commonly used amide local anaesthetic bupivacaine produces prolonged intense sensory and motor block with significant sympathetic blockade and excellent surgical relaxation [4, 5]. But at the commonly used dosage, it produce more undesirable side effects[6]: By reducing the dosage, bupivacaine limits its distribution of spinal block and causes comparably rapid recovery[7].

In the last two decades the concept and choice of adding adjuvant to local anaesthetic agents in spinal anaesthesia have been raised. These adjuvants not only reduce the undesirable hemodynamic effects of spinal anaesthesia, by lowering the requirement of local anaesthetic dose but also provide satisfactory block [8,9]. They also have "synergistic antinocioceptive

effect″ along with intrathecal local anaesthetic both during intra operative and post operative periods by extending analgesia duration[10].

Fentanyl is a lipophilic μ receptor opioid agonist. Intrathecal fentanyl as adjuvant to local anaesthetic has a rapid onset of action and significantly reduces visceral and somatic pain which have been proved in various studies [11, 12]. Lots of studies have been conducted using fentanyl as adjuvant in caesarian section in various routes[13]. Though intrathecal fentanyl gives better quality of analgesia and duration, it is also associated with significant pruritis[14].

Dexmedetomidine is highly selective α 2 agonist, which has been used as a short term sedative agent for mechanically ventilated ICU patients. Off late it has been used as neuraxial adjuvant for caesarean section and labor analgesia because of it stable hemodynamics, potent intraoperative and prolonged post operative analgesic properties with lesser incidence of maternal and neonatal complications[15].

Although there are several studies that includes comparison of dexmedetomidine and fentanyl as adjuvant, very few studies have been conducted on caesarean section[9,14]. As the characteristics of dexmedetomidine would be suitable for parturients who have altered physiology even after delivery, this study was designed to compare the effects of addition of Dexmedetomidine and fentanyl to hyperbaric bupivacaine 0.5% for elective lower segment caesarean section (LSCS).

AIM OF THE STUDY

To evaluate and compare two groups - intrathecal dexmedetomidine and intrathecal fentanyl as adjuvant to 0.5% hyperbaric bupivacaine in elective caesarean section, with respect to:

1. Sensory and motor blockade - onset and duration.
2. Sedation.
3. Hemodynamic changes.
4. Time for post operative rescue analgesia.

BASIC SCIENCE

ANATOMY

Central neuraxial blockade produces predictable sympathetic blockade, sensory analgesia or anaesthesia and motor blockade. Neuraxial block depends mainly on the volume, dose and concentration of local anaesthetic injected into the subarachnoid space. Before going into technique of performing spinal anaesthesia three dimensional understanding of anatomy is must[16].

The spinal cord and its nerve roots are contained within the vertebral (spinal) canal, a bony structure that extends from the foramen magnum to the sacral hiatus. There are seven cervical, twelve thoracic and five lumbar vertebrae called the true vertebra. The sacrum comprises five and the coccyx four fused segments called the false vertebra.

The adult spine presents four curvatures. These curvatures are of major importance to the distribution of local anaesthetic solution in the subarachnoid space. The bony vertebral canal creates a barrier to an advancing spinal needle.

. The vertebrae are held together by Intervertebral discs and series of overlapping ligaments namely[17, 18]

- Anterior longitudinal ligament
- Posterior longitudinal ligament
- Ligamentum flavum
- Interspinous ligament
- Supraspinous ligament

There are certain common palpable landmarks that may correspond to particular level, including the most prominent spinous process which usually corresponds to the seventh cervical vertebra. The inferior angle of scapula usually corresponds to the seventh thoracic vertebra. Tuffier line, the line connecting the two iliac crests almost crosses the vertebral column at the level of L4-L5 intervertebral space principal landmark used to determine the level for insertion of a needle intended to produce spinal anaesthesia[17]. Successful neuraxial block is thus critically dependent on the anaesthesia provider's appreciation of the anatomy of this structure.

The intervertebral canal consists of[19]:

1. Roots of spinal nerves

2. Spinal membrane with the spinal cord and cerebrospinal fluid

3. Vessels, fat and areolar tissue.

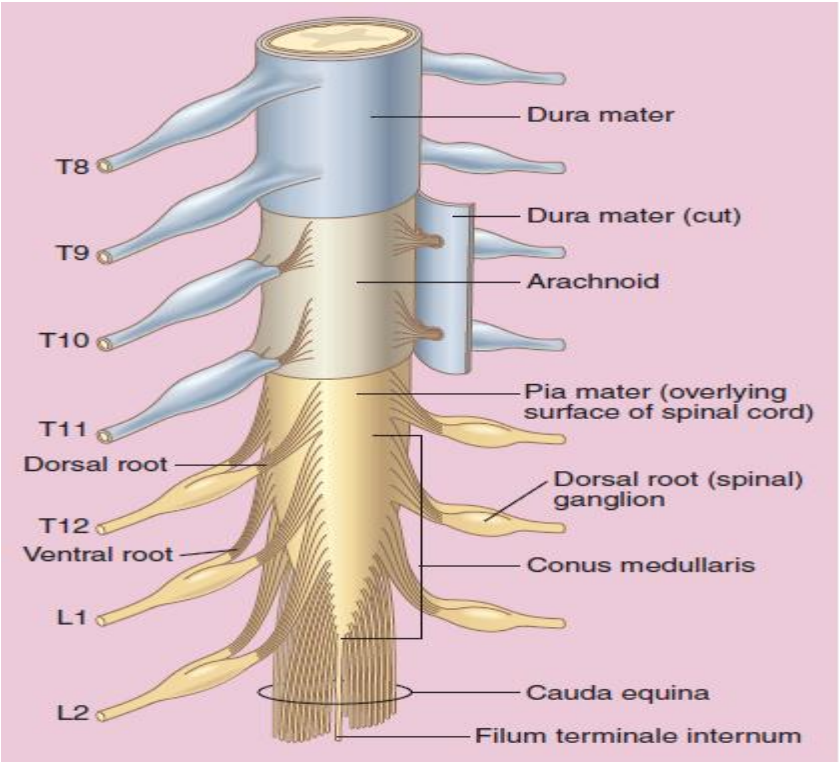


Fig 1: Coverings of spinal cord

The spinal cord begins at the rostral border of the medulla at the upper border of atlas and terminates distally in the conus medullaris as in fig 1[16,19,20]. Because of the differential growth rates between bony vertebral canal and spinal cord, cord terminates much higher than the bony canal. Length of cord Varies from entire canal length in foetus, upto L3 in infants and up to lower border of L1 in adults. Below the conus, the roots are oriented parallel to this axis and resemble a horse's tail, from which the name cauda equina is derived.

The spinal cord is surrounded and protected by three layers of connective tissue known as the meninges (**fig 1**)[19].

- ✓ duramater
- ✓ arachnoid mater
- ✓ piamater

The duramater is a tough fibro elastic membrane attached to the margins of foramen magnum above as an extension of cranial dura and ends at the lower border of the second sacral vertebra. The anterior and posterior nerve roots from the spinal cord pierce the investing layer of duramater.

The arachnoid mater is a thin transparent sheath closely adherent to the inner surface of the dura, imparts impermeability. It serves as the major pharmacologic barrier preventing movement of drug from the epidural to the subarachnoid space.

The piamater is a highly vascular layer closely adherent on the cord and sends delicate septa into its substances. Inferiorly the piamater ends as a prolongation termed as filum terminale which penetrates the distal end of dural sac and is attached to the periostium of coccyx.

The subarachnoid space lies between the arachnoid and the pia and is filled with the cerebrospinal fluid formed from the choroid plexus of lateral, third and forth ventricle. It contains the spinal nerve roots and the denticulate ligament. Lumbar puncture is routinely done below the second lumbar vertebra to L3-L4 interspace to avoid damaging the spinal cord which ends at the lower border of first lumbar vertebra.

Blood supply of spinal cord[20]

Three longitudinal arterial channels supply the spinal cord

- ✓ One anterior spinal artery
- ✓ Two posterior spinal arteries

The main source of blood supply to the spinal arteries is from the vertebral arteries. However it reaches only up to the cervical segment of the cord. Posterior spinal arteries emerge from the cranial vault and supply the dorsal (sensory) portion of the spinal cord have rich collateral anastomotic links from the subclavian and intercostal arteries, this area of the spinal cord is relatively protected from ischemic damage. The spinal arteries also receive blood through radicular arteries accompanying the roots of spinal nerves.

Only few of these radicular arteries are larger in size. A highly variable artery, arteria radicularis magna, or artery of Adamkiewicz, arises from the aorta in the lower thoracic or upper lumbar region, the largest of the radicular arteries and it may be responsible for supplying blood to as the lower two-thirds of the spinal cord. Injury of it will cause anterior spinal artery syndrome. The anterior and the posterior spinal arteries do not have any anastomosis. So thrombosis in any of these arteries will cause spinal cord infarction.

Venous drainage of the spinal cord is through six longitudinal venous channels.

- Unpaired anteromedian and posteromedian venous channels
- Two paired anterolateral and posterolateral channels.

These channels join together and form a venous plexus, from here the venous blood drains through the radicular vein into segmental veins; the vertebral veins in the neck, the azygos veins in the thorax, lumbar veins in the abdomen and lateral sacral veins in the pelvis. These veins are prominent in the lateral epidural space and ultimately empty into the azygos venous system.

Spinal nerves

. Distal to the dorsal root ganglion, nerve roots merge to form 31 pairs of spinal nerves (8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal). Because the sensory fibers traverse the posterior aspect of the subarachnoid space, they tend to lie dependent in a supine patient, thus making them particularly vulnerable to hyperbaric (heavier than CSF) solutions containing local anaesthetic[17]. The dura becomes thinned as it traverses this area (often called the dural sleeve), thereby facilitating penetration of local anaesthetic[19, 20]. The onset of spinal block by local anaesthetics thus occurs by blockade of sodium ion conductance in this region. The area of skin innervated by each spinal nerve is called a dermatome. The lower nerve roots descend before exiting the intervertebral foramen; the spinal cord terminations of the afferent fibers from each dermatome are more rostral than their corresponding vertebral level.

PHYSIOLOGY

CSF Circulation[17]

Cerebrospinal fluid was described by Galen as colorless fluid filling the ventricles. Weed first described that the choroid plexus in the ventricles as the site of production of CSF. CSF is secreted at rate of 0.3 to 0.5 ml/min. The average volume ranges from 120 to 150 ml, 25 ml of which is in the cerebral subarachnoid space, 35 ml in the ventricles and spinal subarachnoid space contains about 75 ml.

CSF Pathways[19]

CSF transverses from the lateral ventricles by the foramen of Monro into the third ventricle and from there in to the fourth ventricle through the aqueduct of sylvius. It reaches the subarachnoid space from the fourth ventricle through the median foramen of magendie and the lateral foraminae of Luschka. The only functional communication between the cerebral ventricles and the subarachnoid space is at the fourth ventricle. It bathes the brain and spinal cord.

CSF Absorption

The absorption of the cerebrospinal fluid is a dual process, being chiefly a rapid drainage through the arachnoid villi and arachnoid granulations of superior saggital sinus and its lateral lacunae into the great dural sinuses with a small contribution through a slow escape into the true

lymphatic vessels by a perineural course. About 300-380 ml of cerebrospinal fluid enters venous circulation per day.

Physical properties of CSF are:

pH: 7.32

Specific gravity at body temperature: 1.002-1.009

Specific gravity at 4 degree Celsius: 1.0003

Density: 1.0003gm/ml

Baricity: 1.000

CSF pressure: 50-180mm of H20

CSF plays an important role in spinal anaesthesia as a media for dispersion of the local anaesthetic drug along the spinal nerve. Specific gravity of the injected solution determines the spread of the local anaesthetic drug in the subarachnoid space.

PHARMACOLOGY

LOCAL ANAESTHETICS

Local anaesthetics are drugs that produce reversible conduction blockade of impulses along central and peripheral nerve pathways after regional anaesthesia. When local anaesthetic solutions are injected into the subarachnoid space they act on superficial layers of spinal cord, predominant site being preganaglionic fibers of the anterior rami. It produces conduction block of small diameter, unmyelinated symphatetic fibers before interrupting conduction in myelinated sensory & motor fibers[21].

Zone of Differential Blockade

In subarachnoid block, sympathetic fibers are blocked two to six dermatomes higher than the sensory fibers. Motor block will be two dermatomes below the sensory block[21].

Pharmacokinetics

The uptake of local anaesthetics from subarachnoid space into neuronal tissue depends on four factors

- ✓ Concentration of local anaesthetics in CSF
- ✓ Surface area of nerve tissue exposed to CSF
- ✓ Lipid content of nerve tissue
- ✓ Blood flow to nerve tissue

Mechanism for uptake of local anaesthetics is by diffusion from CSF into spinal cord & by extension into spaces of Virchow-Robin.

Baricity is a ratio comparing the density of a local anaesthetic solution at a specific temperature to the density of CSF at the same temperature. Baricity places a important role in determining the spread & distribution of local anaesthetics in the CSF.

Hypobaric solutions have a Baricity of less than 1 relative to CSF and are excellent choice for procedures in perineal or in prone jack knife positions.

Isobaric solutions have Baricity equal to 1 and are as dense as CSF and patient positioning does not affect the spread in case of isobaric local anaesthetics. Gravity does not play a role in the spread.

Hyperbaric solutions have Baricity more than 1 relative to CSF and are denser than CSF and they tend to follow gravity, so positioning affects the spread of local anaesthetics.

Indications of subarachnoid block

Spinal anaesthesia can be given for following surgeries below umbilicus

- ✓ Obstetric procedures.
- ✓ Gynecological procedures.
- ✓ Lower abdominal surgeries.

- ✓ Lower limb surgeries.
- ✓ Urological procedures.
- ✓ Perineal & rectal surgeries.

Contraindications of subarachnoid block

Absolute contraindications:

- Patient refusal.
- Infection at the site of injection.
- Hypovolemia.
- Coagulopathy.
- Increased intracranial pressure.
- Indeterminate neurologic disease.

Relative contraindications:

- Infection distant from anatomic site of puncture.
- Unknown duration of surgery.
- Certain cardiac diseases if level above T6 are required.
- Major spine deformities or previous spine surgeries.
- Allergy to local anaesthetics.

Factors determining local anaesthetic spread[22]

Properties of local anaesthetics

- ✓ Baricity
- ✓ Dose

- ✓ Volume
- ✓ Specific gravity
- ✓ Concentration

Patient Characteristics

- ✓ Height
- ✓ Position during & after injection
- ✓ Spinal column anatomy

CSF Characteristics

- ✓ CSF composition
- ✓ CSF volume

Technique of injection

- ✓ Site of injection
- ✓ Direction of needle
- ✓ Direction of bevel

Complications of subarachnoid block

- ➢ High or total spinal anaesthesia
- ➢ Failed spinal
- ➢ Patchy block or inadequate anaesthesia
- ➢ Intravascular injection
- ➢ Neurotoxicity
- ➢ Transient neurological symptoms
- ➢ PPDH

- Cardiovascular collapse
- Back pain
- Arachanoiditis
- Cauda equine syndrome

SPINAL ANAESTHESIA FOR CAESAREAN SCETION

With increasing incidence of caesarean section the selection of an anaesthetic technique depends on surgical, maternal and anaesthetic factors. Either general anaesthesia or regional anaesthesia can be administered for Caesarean section. Regional anaesthesia is the most commonly preferred technique accounting to its better safety profile[23]. Spinal Anaesthesia is most preferred as it has several advantages for anesthetist and surgeons as well as beneficial for mother and baby[3].

Advantages

✓ **General Factors**[2]

- Simplicity and reliability
- Economical
- Rapid onset
- Less systemic toxicity
- Excellent pain relief

✓ **Maternal Factors**[24,25]

- Avoids airway manipulation

- Less postoperative nausea and vomiting
- Better respiratory function
- Less thromboembolic risk
- Early return of GI function
- Earlier mother infant bonding
- Reduces hospital stay
- Reduces risk of morbidity and mortality
- Reduces splinting hence increased oxygenation
- Parturient remains awake hence less chance of aspiration
- Effective postoperative pain relief
- Suppresses pain mediated stress response of surgery
- Reduces amount of surgical hemorrhage
- Excellent muscle relaxation for good operating condition

✓ **Fetal factors**

- Reduced drug exposure
- Placental perfusion maintained
- Reduced neonatal respiratory depression
- Reduced neonatal need for resuscitation
- Neuro-behavioral assessment are better

Disadvantages

- Bradycardia

- Hypotension
- Shivering
- Intra operative and postoperative nausea and vomiting
- Difficulty in performing subarachnoid block
- Not suitable if surgery is expected to be prolonged as it has limited duration of action.
- Intracranial infection
- Postdural puncture headache

In case of higher level of blockade there may be more incidence of bradycardia,rarely may lead to high spinal or total spinal anaesthesia. Maternal hypotension being the most common problems following spinal anaesthesia can be effectively prevented by adequate preloading with 750-1000 ml of crystalloids, prophylactic vasopressors, using low dose of local anaesthetic agent, minimizing aorto-caval compression and sufficient co-loading[26].

Shivering is a troublesome side effect for mother and an anesthetist. It increases maternal O_2 consumption and metabolic demand. Nausea and vomiting is very common and unpleasant event following spinal anaesthesia. Multiple etiologies are being suggested such as hypotension, vagal hyperactivity, visceral pain and intravenous opioids. Antacid prophylaxis and antiemetics are useful prophylaxis. Correction of

hypotension with concomitant antiemetics remains the main mode of treatment.

Spinal anaesthesia for Caesarean section this conveys a significant advantage over general anaesthesia because of its simplicity and rapid onset of action[3]. It also does not have any long term risk of life threatening morbidity or mortality.

Local Anaesthetics

Local anesthestics are injected into CSF , it bathes the nerve root in the subarachanoid space. This allows a relatively small dose & volume to achieve dense sensory & motor blockade. Blockade of conduction in the posterior nerve root fibres interrupts somatic & visceral sensation , whereas anterior prevents efferent motor & autonomic outflow. Choice of local anaesthetics is based on potency of the drug, onset and duration of anaesthesia & side effects of the drug[27].

Fate of local anaesthetics in subarachnoid space

Blood flow determines the rate of removal of local anaesthetics from spinal cord tissue. Elimination of local anaesthetics from subarachnoid space is by vascular absorption from epidural space & subarachnoid space. Faster the blood flows in spinal cord, more rapid the anaesthetic drug is washed away.

PHARMACOLOGY OF BUPIVACAINE[30]

Bupivacaine, long acting amino amide local anaesthetic was first synthesized in Sweden by A.F Ekenstam and his colleagues in 1957. "First report of its use was in 1963 by L.J Teluvio". It is one of the widely used local anaesthetic agents extensively used for intrathecal, extradural and peripheral nerve blocks, with or without motor blockade depending on the concentration.

Chemical structure of bupivacaine

Bupivacaine has an IUPAC nomenclature of 1-butyl-n-(2, 6-dimethylphenyl) piperidine-2-carboxamide. Bupivacaine is characterized by PIPECO-LOXYLIDIDES. It is chiral drug with one asymmetric carbon atom so they exist as enatiomers as depicted in fig 2.Commercially available Bupivacaine is a 50:50 racemic mixture of the enatiomers.

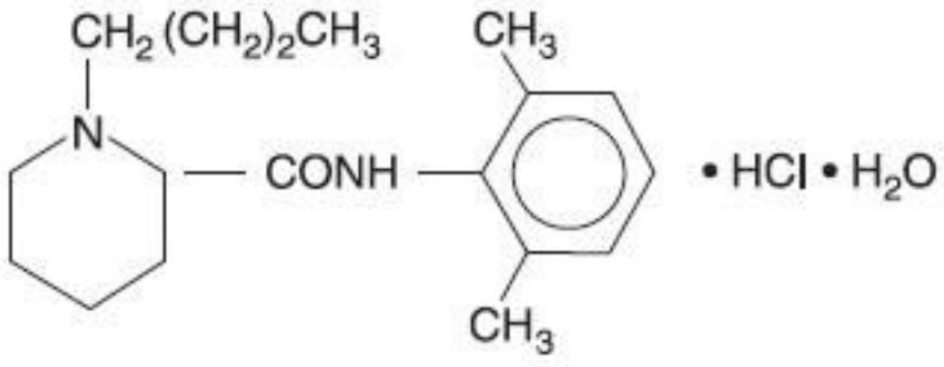


fig 2: chemical structure of bupivacaine

Physical properties: Bupivacaine is a highly lipid soluble local anaesthetics, slow onset & longer duration of action. It is highly potent, 4 times that of lignocaine.

Molecular formula: C18 H28 N2O HCl

Molecular weight: 288.43 g/mol

Volume of distribution: 73 liters, Lipid solubility: 28, Clearance: 0.47litre/min. Protein binding: 95%, pH of saturated solution: 5.2, pKa: 8.1 Duration of action: 240-480min, Elimination t1/2: 210mins, Maximum single dose: 175mg

Toxic plasma concentration: >3mcg/ml

Mechanism of action[29]

Mechanism of action of Bupivacaine is similar to that of any other local anaesthetic, produce electrical stabilization of axon by interfering with normal functioning of Na+ ion channel of nerve membrane thus inhibiting the transmission of nerve impulses (conduction blockade). Sodium channel is a protein embedded in the lipid rich bilayer. Failure of sodium ion channel permeability slows the rate of depolarization such that threshold potential is not reached and thus an action potential is not propagated. Local anaesthetics do not alter the resting transmembrane potential or threshold potential.

The mechanism by which local anaesthetics block sodium conductance:

- Local anaesthetics in the unpronated cationic form acts on the receptors within the sodium channels on cell membrane and block it. The local anaesthetics can reach the sodium channel either via the lipophilic pathway directly across the lipid membrane or via the axoplasmic opening. This mechanism accounts for 90% of the nerve blocking effects of amide local anaesthetics.
- The second mechanism of action is by membrane expansion. This is a nonspecific drug receptor interaction.

Other site of action are Voltage dependent potassium ion channels, Calcium ion currents (L-type most sensitive) and G protein coupled receptors.

Maximum dosage - 3mg/kg body weight

Availability-

Commercial preparation is produced as hydrochloride salts.

Ampoules: - 0.5% Bupivacaine hydrochloride 4cc.

0.5% Bupivacaine with dextrose (heavy) 4cc.

Vials - 0.25% & 0.5% Bupivacaine hydrochloride 30cc.

Anaesthetic potency[21]

All local anaesthetics are weak bases having pKa above physiological pH. Local anaesthetics with pKa nearest to physiological pH have more rapid onset. Hydrophobicity appears to be a primary determinant of intrinsic anaesthetic potency and Bupivacaine is highly hydrophobic, hence it is 4

times more potent than lignocaine. Intrinsic vasodilatation activity also determines the duration of action and potency of Bupivacaine.

Onset of action:-

As the pKa is around 8 the unionized form is less compared to lignocaine, so the onset of action is delayed. The onset of conduction blockade is dependent on the dose or concentration of local anaesthetics and route of administration. The onset of action of Bupivacaine in spinal anaesthesia is between 4-6 mins and maximum anaesthesia is obtained between 15-20minutes.

Pharmacokinetics

The plasma concentration of Bupivacaine is determined by the amount injected, the rate of absorption from the site of injection, the rate of tissue distribution and the rate of biotransformation and excretion. Also depends on adjuvant such as sodium bicarbonate and adrenaline. The site of injection is the major determinant of all. Bupivacaine is the slowest to be metabolized among amide LA. Bupivacaine can be detected in the blood within 5 minutes of infiltration or following epidural or intercostal nerve blocks. Plasma concentration depends on rate of tissue distribution and rate of clearance. Lipid solubility is the primary determinant of redistribution. Plasma level is related to the total dose administered. Peak levels of 0.14 to 1.18 μg/ml were found within 5 minutes to 2 hours, and they gradually declined to 0.1 to 0.34 μg/ml by 4 hours. Predominant mechanism of

termination of block is by systemic absorption and subsequent metabolism and excretion.

Plasma binding:

Plasma binding parallels the lipid solubility and inversely related to plasma concentration. In plasma, drug binds avidly with protein, α1-acid glycoprotein which is the most important plasma protein site to extent of 70-80%. Binding reduced free drug thus reduces the incidence of systemic side effects.

Lung extraction

Lungs are capable of extracting Bupivacaine after rapid increase in plasma concentration. This first pass pulmonary extraction is dose dependent as it gets rapidly saturated.

Absorption

The systemic absorption of Bupivacaine is determined by the site of injection, Vascularity of site, lipid solubility, dose and addition of a vasoconstrictor. Absorption is faster in areas of high Vascularity especially in intercostals areas.

Metabolism:-

Bupivacaine undergoes enzymatic degradation primarily in the liver by microsomal enzymes, by aromatic hydroxylation, N-dealkylation amide hydrolysis and conjugation. . Rate of metabolism depends on hepatic extraction ratio, hepatic blood flow and also on competition for intrahepatic

enzymatic pathway. The excretion occurs primarily via the kidney. Renal perfusion and factors affecting urinary pH affect urinary excretion. Less than 5% of Bupivacaine is excreted via the kidney unchanged through urine.

The major portion of injected agent appears in urine in the form of 2, 6 pipecolyoxylidine (ppx) which is a n-dealkylated metabolite of bupivacaine As the metabolism is slow cumulative, drug effects and systemic toxicity are more likely with repeated continuous administration.

Toxicity:-

Plasma concentrated determined by rate of drug entrance into systemic circulation, clearance and metabolism. The toxic plasma concentration is set 4-5mcg/ml. Maximum plasma concentration rarely approach toxic levels. .

Distribution:

Two phase rapid (α) and slow (β), In rapid phase the drug is distributed to highly vascular organ half life being 2.7 minutes whereas in slow phase the drug distributes to slowly equilibrating tissues and half life being 28 minutes.

Biotransformation and excretion:-

Half life of delta is 3.5 hours, clearance is 0.47litre/minute. More highly perfused organs show higher concentration of the drug. Bupivacaine is rapidly excreted by lung tissue. Though skeletal muscle does not show any particular affinity for bupivacaine it is the largest reservoir of the drug.

Pharmacodynamics:

Central Nervous System

Bupivacaine readily crosses the blood brain barrier causing CNS depression following higher doses. The initial symptoms involve feeling of light-headedness and dizziness followed by visual and auditory disturbances. Disorientation and drowsiness may occur. Objective signs are usually excitatory in nature, which includes shivering, muscular twitches and tremors, initially involving muscles of the face (perioral numbness) and part of extremities. At still higher doses cardiovascular or respiratory arrest may occur

Autonomic Nervous System

Bupivacaine does not inhibit the noradrenaline uptake and hence has no sympathetic potentiating effect. Myelinated preganglionic B fibers have a faster conduction time and are more sensitive to action of Bupivacaine. When used for conduction blockade, all local anaesthetics, particularly Bupivacaine produces higher incidence of sensory than motor fibers.

Cardiovascular System

The primary cardiac electrophysiological effect of a local anaesthetic is a decrease in the maximum rate of depolarization in Purkinje fibers and ventricular muscle. This action by Bupivacaine is far greater compared to Lignocaine. Also, the rate of recovery of block is slower with Bupivacaine.

Therefore Bupivacaine is highly arrythmogenic. Bupivacaine reduces the cardiac contractility by blocking the calcium transport.

Respiratory System

Respiratory depression may be caused if excessive plasma level is reached which in turn results in depression of medullary receptor center. Respiratory depression may be also caused by paralysis of respiratory muscles of diaphragm as may occur in high spinal or total spinal anaesthesia.

Adverse Effects are encountered in clinical practice mostly due to overdose, inadvertent intravascular injection or slow metabolic degradation. Allergic reactions may present as Urticaria, bronchospasm and hypotension.

PHARAMACOLOGY OF FENTAYL[30, 31]

Fentanyl is a synthetic opioid receptor agonist which is 75-125 times more potent than morphine.

Chemical structure

PHENYL PHERIDINE DERIVATIVE with nucleus containing PHENANTHERENE structure as in fig 3.

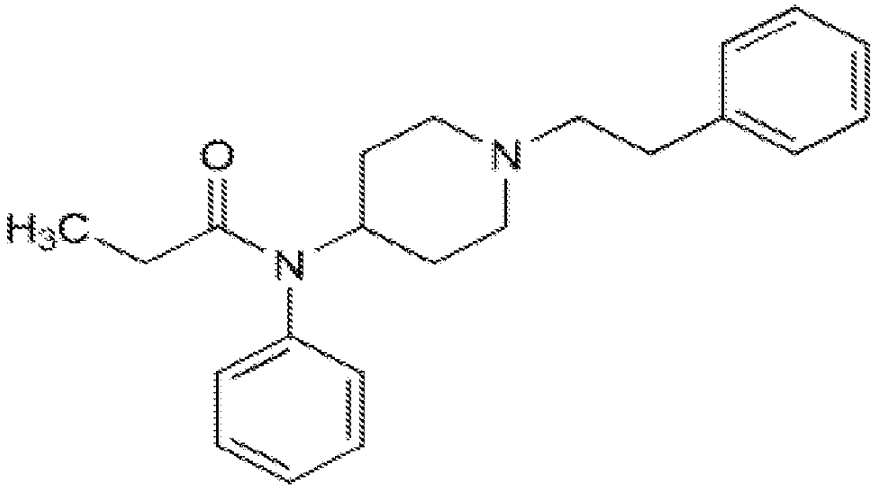


Fig 3: Chemical structure of fentanyl

Mechanism of action

It is a highly lipophilic synthetic compound with pure agonist action on stereotypic μ type opioid receptor at presynaptic and post synaptic sites of central nervous system and peripheral tissue. Opioid activation cause presynaptic inhibition of neurotransmitter (Ach, Dopamine, Norepinephrine, substance P) release by increasing potassium conductance and calcium channel inactivation. It also inhibits the release of excitatory

neurotransmitter like substance P. It produces effect by inhibiting adenylcyclase hence decrease neurotransmitter release.

Dose and mode of administration

It is a major component of balanced anaesthesia

1-2mcg/kg intravenous ⟹ analgesia

25mcg (maximum) ⟹ intrathecal

5-20mcg/kg ⟹ oral/transmucosal

75-100mcg/hr ⟹ transdermal

Plasma concentration should be around **20-30ngm/ml** for maximum analgesia.

Pharmacokinetics

Very highly lipiophilic, so crosses the blood brain barrier easily, hence has rapid onset of action and greater potency. Volume of distribution is very high; hence it is very short acting. It gets rapidly distributed to fat, skeletal muscles and pulmonary tissue. So with continuous infusion or multiple dosages the saturation of tissue occurs & will produce prolonged duration of action. Intrathecal fentanyl produces selective segmental analgesia by blocking opioid receptors of dorsal horn. The duration and amount of analgesia depends upon the drug concentration. Lower dose of fentanyl is required for intrathecal administration than the systemic dose, so the side effects are minimal. But some systemic side effects do occur

because of cephalad migration of drug and vascular or tissue uptake. Fentanyl is a smaller molecule and lipophilic hence readily crosses placenta.

pKa—8.4, Protein binding-80%, Clearance-1530ml/min, Volume of distribution- 335litres, Elimination half life- 31.66 hrs

Context sensitive half life after 4 hours of infusion- 260 minutes

Metabolism

90% metabolized in liver by N-Demethylation to produce Nor-fentanyl, hyroxy proprionyl fentanyl, hyroxy Proprionyl nor fentanyl. These products are minimally active.

Excretion

Excretion is mainly by kidney. Only 10% of it is excreted unmetabolized.

Metabolites are seen in urine even after 72 hours.

Elimination half life

80% leaves plasma in less than 5 minutes as it is highly lipid soluble it is largely distributed. The plasma concentration is reached only by redistribution hence has a longer half life.

Context sensitive half life

It is prolonged if the drug is given as infusion for greater than 2 hours as the peripheral tissues become saturated.

Pharmacodynamics

Central Nervous System

Rapid IV injection may produce seizure like activity. By EEG monitoring they were found to be myoclonus due to inhibition neurons of temporal lobe. It produces skeletal muscle rigidity. At normal $Paco_2$ it produces rise in intracranial pressure by 6-9mmhg associated with fall in mean arterial pressure and cerebral perfusion pressure due to autoregulatory reduction in cerebral vascular resistance.. Muscle rigidity is caused by μ receptors of brain stem midline nuclei & basal ganglia.

Cardiovascular System

Fentanyl depresses isolated myocardial contractility at high dose, but does not produce direct myocardial depression at normal dose. Carotid sinus baroreceptor reflex control of heart rate is markedly depressed by fentanyl. There is no histamine release as with other opioids such as morphine or pethidine. Its vagomimmetic action produces dose dependent fall in heart rate, even severe bradycardia or asystole is noted at high doses. By suppression of central sympathetic outflow it produces dose dependent fall in blood pressure.

Respiratory System

There is dose dependent suppression of respiratory centre causing reduction in tidal volume and minute ventilation. Severe delayed respiratory

depression occurs in the post operative period due to the redistribution of the drug from the peripheral tissue.

Gastrointestinal System

It decreases gastrointestinal motility hence causes constipation. By direct stimulation of chemoreceptor trigger zone, it produces nausea and vomiting.

Pruritis

It produces intense pruritis which seems to be mediated by μ type opioid receptor.

Uses

- ✓ Sedation in ICU setup
- ✓ Surgical analgesia
- ✓ Along with inhalation agents in balanced anaesthesia
- ✓ High dose in IHD patients as induction
- ✓ Blunting intubation stress response
- ✓ As adjuvant in regional anaesthesia

Adverse Effects

Persistent or recurrent respiratory depression in post operative periods, prominent fall in heart rate, fall in blood pressure, rigidity and myoclonus, raised ICP, reflex coughing

PHARMACOLOGY OF DEXMEDETOMIDINE[32, 33]

Dexmetedomidine is active dextro enatiomer of medetomidine, methylsted derivative of etomidine[32]. It is chemically related to clonidine, but more selective α_2 adrenoreceptor agonist with 1620 greater selectivity for α_2 receptors compared to α_1 receptors. In 1999, FDA approved it as sedative and supplement to sedative in mechanically ventilated patients in ICU settings. It is now being used in various settings outside ICU, including total anaesthesia in adults and children in minimally invasive procedures, sedation for diagnostic procedures and other applications[33].

Chemical structure

It is chemically described as 4-S-[1-(2,3 dimethylphenyl)ethyl] -1 H-imidazole monohydrochloride

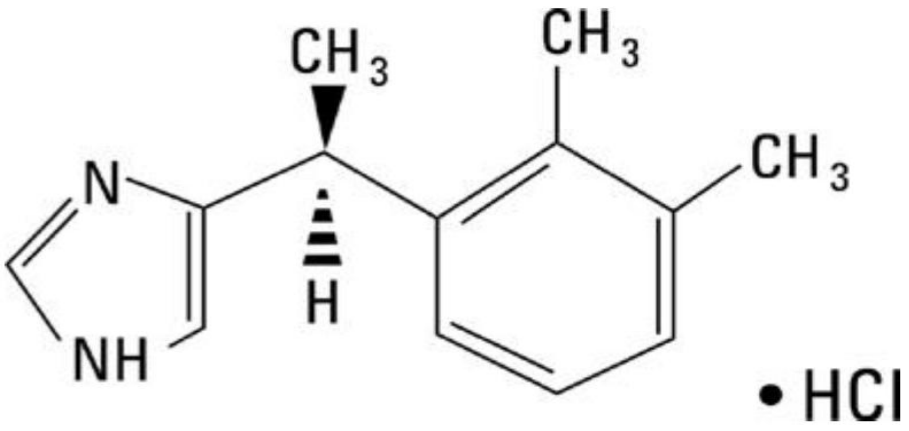


FIG 4 : Chemical structure of dexmedetomidine

Physical properties

Molecular weight-236.7, pH:6-7, pKa:7.1

Mechnism of action

The α_2 adrenergic receptors (or adrenoceptors) are transmembrane receptors composed of excitable G-proteins, which cross the cell membrane and link selectively with endogenous mediators or exogenous molecules. The α-2 adrenergic receptor consists of 3 α-2 isoreceptors - α-2a, α-2b and α-2c - which bind α-2 agonists and antagonists with similar affinities. Varied pharmacodynamic effects of dexmedetomidine are mediated by Specific α-2 receptor subtypes. Physiological responses regulated by α 2 receptor varies depending on their location. Stimulation in brain and spinal cord inhibit neuronal firing which leads to hypotension, bradycardia, sedation and analgesia.

Sedative effect is mediated by hyper polarization of nonadrenergeric neurons in locus ceruleus of the brain stem, main site in modulating wakefulness. α_2 receptors inhibit adenylyl cyclase, which catalyses cAMP. Dexmedetomidine by decreasing amount of cAMP favors anabolic pathways. The analgesic effects are believed to be in dorsal horn of the spinal cord .In spinal cord it directly reduces the pain transmission by reducing the release of pro-nocioceptive transmitter, substance P and glutamate from primary afferent terminals and hyperpolarizing spinal interneurons by activation of potassium channels.

Pharmacokinetics

It follows zero order kinetics; constant amount of drug is eliminated per hour. When injected intravenously, onset of action starts within 15 minutes with peak concentration being achieved within an hour. It is 94% protein bound and is metabolized in the liver through glucuronide conjugation and biotransformation by cyt P450 enzyme system. Metabolites are eliminated in urine 95% and 4% in feces. Volume of distribution is 118 L, with distribution t1/2 is 6 min in adults and elimination t1/2 is 2-2.5 hours. Clearance is estimated to be 39L/hr. **Dosage:** For adults, it is administered intravenously at loading dose of 0.5-1 mcg/kg as slow infusion followed by maintenance at 0.2-0.7 mcg/kg/hr. It is freely soluble in water. It is diluted in normal saline.

Pharmacodynamics

Cardiovascular System

Dexmedetomedine causes brief biphasic, dose dependent cardiovascular response. It causes decrease in heart rate, myocardial contractility, cardiac output, systemic vascular resistance and blood pressure. Due to stimulation of α2b receptors in vascular smooth muscles, there is initial increase in blood pressure & drop in heart rate after bolus dose of 1mcg/kg. Initial response lasts for 5-10minutes followed by decrease in blood pressure due to inhibition of central sympathetic outflow.

Fall in blood pressure and heart rate are due to decrease in norepinephrine release due to stimulation of α_2 receptors at presynaptic terminals. Dose dependent decrease in heart rate is due to decrease in sympathetic tone , partly by baroreceptor reflex and enhanced vagal activity.

Central Nervous System

It produces sedation, hypnosis, anxiolysis, amnesia and analgesia. It acts on locus ceruleus and causes sedation as well as hypnosis

Analgesia

Analgesic properties are complex and not clearly known. Dorsal horn of spinal cord is major site of analgesic action. It appears to exert analgesic properties at spinal cord level and at supraspinal sites.

Respiratory System

Despite sedative properties, dexmedetomidine is associated with limited respiratory effects, reduces minute ventilation though the response to increase in co_2 concentration is preserved. Apnea threshold is actually decreased.

Clinical applications

Dexmedetomidine is used as sedation in ICU patients, also as sole anaesthetic agent in monitored anaesthesia care. It is also used as premedicant, also as an adjunct with local anaesthetics in peripheral nerve blocks, intravenous regional anaesthesia and spinal anaesthesia

Anaesthesia

When used as a premedicant it reduces the requirements of induction agents (30%), Opioid and volatile anaesthetics (25%). It has been used as an adjuvant to general anaesthesia. It suppresses the hemodynamic response (hypotension and bradycardia) when administered as premedicant at desired dose. In neurosurgeries, craniotomy where neurocognitive testing is necessary during surgical procedure, dexmedetomidine seems to better option than general anaesthesia. It is proven to have used in reducing pulmonary hypertension in patients undergoing mitral valve replacement. In morbid obese patients undergoing bariatric surgeries, dexmedetomidine appears to attenuate postoperative pain relief and reduce opioid requirements without causing respiratory depression. It has been used in treatment of withdrawal of narcotics, benzodiazepines and alcohol.

Sedation in Intensive Care Units

Dexmedetomidine has been ideal drug to be used as sedation in ICU settings. It allows sedated patients to be quickly aroused without any discontinuation prior to weaning. It reduces opioid consumption(50%) and significantly high Pao2/Fio2 ratio. Also used in pediatric in procedural sedation

ADVERSE EFFECTS

Transisent hypertension, hypotension, nausea, bradycardia, atrial fibrillation, AV block, delirium and Dry mouth

REVIEW OF LITERATURE

Biswas et al (2002)[6] studied the analgesic effect of intrathecal fentanyl added to bupivacaine in 40 patients undergoing caesarean section. Patients were randomly allocated to receiver either 2 ml of 0.5% inj bupivacaine with 0.25 ml of normal saline (group A, n=20) or 0.25 ml (12.5 µgm) fentanyl with 2 ml of 0.5% inj bupivacaine (group B, n=20). Vital signs, sensory level, motor block, pain score and side effects were observed. Complete analgesia (time from injection to first report of pain) lasted longer in group B (183±9) than group A (129±9.5). The duration of effective analgesia (time from injection to first parenteral analgesic) was increased in group B (248±11.76). They **concluded** that 12.5 µgm of intrathecal fentanyl markedly improve intra operative anaesthesia and significantly reduces the demand for postoperative analgesia. Pruritis was only 15% in fentanyl group.

S kiran et al[34] **(2002)** conducted a randomized double-blind comparison of three doses (7.5 mg, 8.75 mg and 10 mg) of 0.5% hyperbaric bupivacaine in women undergoing elective caesarean under spinal anaesthesia 60 patients allocated in to 3 groups A, B and C respectively. The time to maximum sensory blockade did not differ among the groups ($P \geq 0.05$). Mean time to start of regression of sensory block and Time

required for complete regression of sensory block was longer in group C than in groups A and B ($P \leq 0.001$, $P \leq 0.05$ and $P \leq 0.001$ respectively).

Duration of motor block was greater in group C than in groups A and B ($P \leq 0.001$ and ≤ 0.05 respectively). Neonatal outcome was good in all the groups. The incidence of hypotension was greater in groups B and C than in group A ($P \leq 0.05$). Group C women had a greater incidence of bradycardia than did groups A and B ($P \leq 0.05$). They **concluded** that *7.5-mg dose of 0.5% hyperbaric bupivacaine was observed to provide acceptable analgesia without any significant incidence of adverse effects such as maternal hypotension or bradycardia*.

Al-Ghanem SM et al[9] **(2009)** conducted a study of adding dexmedetomidine (5 µg) or fentanyl (25 µg) to intrathecal **isobaric** bupivacaine (10 mg) in gynecological procedures to evaluate the onset and duration of sensory and motor block as well as operative analgesia and adverse effects. 76 Patients were randomly allocated to receive intrathecally either 10 mg isobaric bupivacaine plus 5 µg dexmedetomidine (group D n = 38) or 10 mg isobaric bupivacaine plus 25 µg fentanyl (group F n = 38). They **observed** that patients in group D had significantly longer sensory and motor block times than patients in group F. The onset times to reach T10 dermatome and to reach peak sensory level as well as onset time to reach modified Bromage 3 motor block were not significantly different between the two groups. The mean time of sensory regression to S1 was longer in

group D than group F (274 ± 73 vs 179 ± 47). The regression time of motor block to reach modified Bromage 0 was longer in group D than group F (240 ± 60 vs 155 ± 46). They **concluded** that in women undergoing gynecological procedure under spinal analgesia, 10 mg plain bupivacaine supplemented with 5 μg dexmedetomidine produced prolonged motor and sensory block compared to 10 mg plain bupivacaine with 25 μg fentanyl.

Mahdy WR et al [35]**(2011)** studied the effects of adding dexmedetomidine (Dxm) (5 μg) versus fentanyl (25 μg) to intrathecal bupivacaine (10 mg) on spinal block characteristics and neonatal outcome in caesarean delivery. 90 females were assigned into three groups: Control group (n = 30) received intrathecal placebo, with bupivacaine 10 mg in 2.5 ml, Dxm group (n = 30) received intrathecal dexmedetomidine 5 μg with bupivacaine 10 mg in 2.5 ml. and Fentanyl group (n = 30) received intrathecal fentanyl 25μg plus bupivacaine 10 mg. in 2.5 ml. They **observed** that onset time to reach peak sensory and motor level were shorter in DXM and Fentanyl groups compared with the control group with no significant difference between DXM and Fentanyl groups. Also DXM group had significantly longer sensory and motor block times than patients in control and Fentanyl group. No adverse effects on mothers or babies were noticed among three groups. They **concluded** that DXM seemed to be an attractive adjuvant to spinal bupivacaine in caesarean section giving good quality of

spinal anaesthesia with minimal side effects and no adverse effects on the babies.

Rajni Gupta et al[14] **(2011)** with an aim to evaluate the onset and duration of sensory and motor block, hemodynamic effect, postoperative analgesia, and adverse effects of dexmedetomidine or fentanyl given intrathecally as adjuvant with hyperbaric 0.5% bupivacaine conducted a study in 60 patients classified in ASA class I and II scheduled for lower abdominal surgeries. Patients were randomly allocated to receive either 12.5 mg hyperbaric bupivacaine plus 5μg dexmedetomidine (group D, n=30) or 12.5 mg hyperbaric bupivacaine plus 25 μg fentanyl (group F, n=30) intrathecal. The mean time of sensory regression to S1 was 476±23 min in group D and 187±12 min in group F(P<0.001). The regression time of motor block to reach modified Bromage 0 was 421±21 min in group D and 149±18 minutes in group F (P<0.001).They **concluded** that intrathecal dexmedetomidine was associated with prolonged motor and sensory block, hemodynamic stability, and reduced demand for rescue analgesics in 24 h as compared to fentanyl.

Rajini Gupta et al[36] **(2011)** studied the effects of dexmedetomidine as an adjuvant to ropivacaine. Patients were randomly allocated to receive intrathecally either 3 ml of 0.75% isobaric ropivacaine + 0.5 ml normal saline (Group R) or 3 ml of 0.75% isobaric ropivacaine + 5 μg dexmedetomidine in 0.5 ml of normal saline (Group D). The mean time of

sensory regression to S2 was 468.3±36.78 minutes in group D and 239.33±16.8 minutes in group R. Duration of analgesia (time to requirement of first rescue analgesic) was significantly prolonged in group D (478.4±20.9 minutes) as compared to group R (241.67±21.67 minutes). They **concluded** that 5µgm dexmedetomidine seems to be an attractive alternative as adjuvant to ropivacaine intrathecally, especially in those requiring longer time as it has excellent quality of postoperative analgesia with minimal side effects.

Hala E A Eid et al [37]**(2011)** aimed to study dose related prolongation of hyperbaric bupivacaine (15mg) spinal anaesthesia by dexmedetomidine in two different doses (10 µg and 15 µg) with respect to duration of sensory and motor block and postoperative analgesic requirements produced by spinal bupivacaine (15 mg). 48 adult patients scheduled for ortho surgeries. Each patient was given 3.5 ml spinal injectate that consisted of 3 ml 0.5% hyperbaric bupivacaine and 0.5 ml containing either 10 µg dexmedetomidine (Group D1), 15 µg dexmedetomidine (D2) or normal saline (Group B). Heart rate, arterial blood pressure, sensory level, motor block, pain and level of sedation were assessed intraoperatively and up to 24 hours after spinal anaesthesia. They found that Dexmedetomidine significantly prolonged time to two segment regression, sensory regression to S1, regression of motor block to modified Bromage 0 and time to first rescue analgesic. In addition, it significantly decreased postoperative pain

scores. In addition, group D2 patients had higher sedation scores and lower postoperative analgesic requirements than Group D1 or B. Hemodynamic stability was maintained in the three groups. They **concluded** that intrathecal dexmedetomidine in doses of 10 μg and 15 μg significantly prolonged the anaesthetic and analgesic effects of spinal hyperbaric bupivacaine in a dose-dependent manner for prolonged complex lower limb surgical procedures.

S Fyneface-Ogan et al [38]**(2012)** purposely conducted a study to determine the effect of adding dexmedetomidine to hyperbaric bupivacaine for neuraxial analgesia for labor. Ninety laboring multiparous women were allocated to have single shot intrathecal bupivacaine alone (B), bupivacaine with fentanyl (BF), or bupivacaine with dexmedetomidine (BD). Sensory and motor block characteristics; time from injection to two dermatome sensory regression, sensory regression to S1 dermatome, and motor block regression to Bromage 1 were recorded. Labor pain was assessed with a 10 cm verbal pain scale. Peak sensory block levels were not significant. The time for sensory and motor blocks to reach T10 dermatome and Bromage 1, respectively, was faster in group BD than in the other groups (P = 0.0001). The time for sensory regression to S1 was significantly prolonged in the group BD (P = 0.0001). Motor block regression time to Bromage 1 was also prolonged in the group BD (P = 0.0001). Neonatal outcome (APGAR) was normal in all groups. They suggested that single shot intrathecal bupivacaine

with dexmedetomidine significantly prolonged sensory block in laboring women.

Vidhi Mahendru et al[39] **(2013)**, with an aim to know the dexmedtomine efficacy as an adjuvant to hyperbaric bupivacaine, conducted a prospective randomized double blinded study in 120 adults of either sex of ASA I and II scheduled for lower limb surgeries. With bupivacaine 12.5mg, group BS was added normal saline, group BF 25µgm fentanyl, group BD with 5 µgm dexmedetomidine and group BC with 30 µgm clonidine. The onset time to reach peak sensory and motor level, the regression time of sensory and motor block, hemodynamic changes, and side effects were recorded. Patients in Group BD had significantly longer sensory and motor block times than patients in Groups BC, BF, and. The mean time of two segment sensory block regression was 147 ± 21 min in Group BD, 117 ± 22 in Group BC, 119 ± 23 in Group BF, and 102 ± 17 in Group BS ($P < 0.0001$). The regression time of motor block to reach modified Bromage zero (0) was 275 ± 25, 199 ± 26, 196 ± 27, 161 ± 20 in Group BD, BC, BF, and BS, respectively ($P < 0.0001$). The onset times to reach T8 dermatome and modified Bromage 3 motor block were not significantly different between the groups. They noted that BD group showed significantly delayed requirement of rescue analgesic. They have **concluded** that the use of intrathecal dexmedetomidine as adjuvant to bupivacaine for long duration

surgical procedures produces profound intra operative anaesthesia and post operative analgesia with minimal side effects.

Hem Anand Nayagam et al [40]**(2014)** conducted a prospective randomized double blind study of intrathecal fentanyl & dexmedetomidine added to **low dose** bupivacaine for spinal anaesthesia for lower abdominal surgeries in 150 patients. Group F (*n* = 75) received bupivacaine 0.5% heavy (0.8 ml) + fentanyl 25 μg (0.5 ml) + normal saline 0.3 ml and Group D (*n* = 75) received bupivacaine 0.5% heavy (0.8 ml) + dexmedetomidine 5 μg (0.05 ml) + normal saline 0.75 ml, aiming for a final concentration of 0.25% of bupivacaine (1.6 ml), administered intrathecally. Time to reach T10 block level, peak sensory block level (PSBL), time to reach peak block level, time to two segment regression (TTSR), the degree of motor block (MBS), side-effects and the time to first analgesic request (TFAR) were recorded. PSBL (*P* = 0.000) and TFAR (*P* = 0.000) were highly significant. Mean time to PSBL (<0.05) and MBS (P = 0.035) were significant. They **concluded** that the clinical advantage of dexmedetomidine over fentanyl was that it facilitated the spread of the block and offered prolonged post operative analgesia compared to fentanyl.

Veena Chatrath et al[41] **(2015)** determined the analgesic efficacy and side effects of adding dexmedetomidine to bupivacaine in spinal anaesthesia for infraumbilical surgeries. Spinal anaesthesia was achieved with 12.5 mg of 0.5% hyperbaric bupivacaine in group B (n = 50) and with 12.5 mg of

0.5% hyperbaric bupivacaine plus 10 μg of dexmedetomidine in group D (n = 50). The two groups were compared with respect to hemodynamic parameters, onset of sensory block to T10 and regression to S1, time to achieve Bromage 3 and regression to Bromage 0, duration of analgesia, number of doses of rescue analgesia required, and complications occurring in 24hr. They have **concluded** that addition of dexmedetomidine to bupivacaine leads to early onset of sensory and motor block with prolonged duration, and patients remained pain free for a longer period with decreased demand for rescue analgesia in the postoperative period as compared with plain bupivacaine.

MATERIALS AND METHODS

The prospective randomized double blinded study was conducted in 60 parturients with ASA physical status I/II undergoing elective lower segment caesarean section under subarachnoid block in Raja Mirasudhar Hospital, attached to Thanjavur Medical College and Hospital, Thanjavur. The study period was from June 2014 to July 2015.

Inclusion criteria:

- Parturient in the age group between 18 and 35 years.
- Parturient belonging to ASA Class I and II.
- Height 140-170 cm.
- Parturient of either primi or mutigravida.
- Parturient with singleton pregnancy of at least 36 weeks.

Exclusion criteria:

- Patients having any absolute contraindications for spinal anaesthesia
- Known hypersensitivity to amide local anaesthetics and study drugs.
- Patients with medical and obstetric complications like heart disease, epileptic, gestational hypertension, gestational diabetes mellitus and hypertension
- Patients with any liver or renal disease

- Known psychiatric illness
- History of chronic intake of painkillers.

After obtaining institutional ethical committee approval and by applying inclusion and exclusion criteria, 60 Parturients were entered in to the study. Every patient was explained in her own language about the purpose and conducting method of the study and an informed written consent was obtained. The documentation was strictly included a detailed history, complete physical examination and investigations such as hemoglobin, blood sugar, renal function parameters, ECG for all patients. Each patient was randomized into either group by using closed cover technique.

Data was collected in pretested proforma meeting the objectives of the study. All patients were premedicated on the night before surgery with tablet ranitidine 150mg, fasted 8 hours for solid food and 4 hours for clear fluids. Intravenous line was secured with 18 guage cannula and the patient was preloaded with 10ml/kg of ringer lactate, half an hour before anaesthesia. All patients received Inj. rantidine 50mg IV and Inj. metoclopramide 10mg IV for aspiration prophylaxis 30 minutes before surgery. Baseline reading of vital parameters was checked in the waiting room. All patients were transported to OT in left lateral position.

In the operating room, anaesthetic machine, equipments for airway management and emergency drugs were kept ready. Horizontal position of

operating table was checked. Patient was connected to electrocardiography (ECG), Non-Invasive Blood Pressure (NIBP) and arterial pulse saturation ($SPO_{2)}$ monitor. Preoperative heart rate, systolic and diastolic blood pressure, mean arterial pressure and oxygen saturation were recorded.

Patients were placed in sitting position. Under aseptic precautions lumbar puncture was performed at the level of L2-L3 or L3-L4 through a midline approach using 25 G Quincke's spinal needle and study drug was injected after confirmation of needle tip in the subarachnoid space by clear and free flow of Cerebrospinal Fluid.

Group A: 0.5% Hyperbaric Bupivacaine 7.5mg (1.5ml) + Dexmedetomidine 5µg (0.5ml).

Group B: 0.5% Hyperbaric Bupivacaine 7.5mg (1.5ml) + Fentanyl 25 µg (0.5ml).

Dexmedetomidine for intrathecal use was prepared by diluting 0.5 ml of drug containing 50 µg to 4.5 ml of normal saline. 0.5 ml of this diluted solution (containing 5 µg) was taken and added to syringe containing 1.5ml 0.5% hyperbaric bupivacaine. The test drugs were prepared by a person not related to the study. Spinal anaesthesia was performed by adequately trained post graduate or by the consultant anaesthesiologist and the data were collected using prescribed proforma.

Patient was made to lie down in the supine posture immediately with the table kept flat horizontally, wedge kept under right hip and supplemental oxygen was given. The time at which spinal anaesthesia performed was noted.

The following parameters were observed and recorded.

1. Onset of motor blockade.
2. Time to complete motor blockade
3. Onset of sensory blockade.
4. Maximum level of sensory blockade attained and the time taken for the same.
5. Time for two segments sensory regression.
6. Sedation score was assessed every 30 minutes intraoperatively and hourly in the postoperative period for first 6 hours using Ramsay sedation score.
7. Systolic and Diastolic blood pressure, Mean Arterial Blood pressure, pulse rate and oxygen saturation were recorded at 0,3,6,9,12 and 15 minutes thereafter every 15 minutes up to 60 minutes.
8. Any discomfort like nausea, vomiting, shivering, pruritus and adverse events such as hypotension, bradycardia, and ECG changes were noted.
9. Neonatal APGAR scores 1 and 5 minutes.

10. Postoperative pain were assessed using Visual analogue scale (0 – 10) at 30 minutes, hourly for the next 6 hours and time to first rescue analgesic request was recorded.
11. Total ephedrine requirement was noted.

After delivery of baby all patients were given inj. oxytocin 10 IU in 500 ml normal saline. At 45 minutes all patients were given inj. ondansetron 4mg IV and inj tramadol 100mg IM. On completion of surgery, patient was shifted initially to Post Anaesthesia Care Unit (PACU) for observation. After stabilization of hemodynamics and complete regression of motor blockade patient was transferred to postoperative ward. Vital signs and oxygen saturation were monitored until recovery of patients from anaesthesia. Injection diclofenac sodium 75mg was given IM when the patient complained of pain in the postoperative period (VAS >3) as Rescue analgesic and time was noted.

DEFINITIONS

Hypotension was said to have occurred if Systolic blood pressure decreased less than 100 mm of Hg or if Diastolic blood pressure decreased less than 50 mm of Hg or if the MAP decreased less than 60 mm of Hg. Patient was treated with 100% O2, increasing the infusion rate of IV fluids and Inj. Ephedrine 6mg at interval of 3-5 minutes.

Bradycardia was defined as heart rate less than 60/min and was treated with intravenous atropine 0.6mg IV.

Sensory block

The **onset of sensory block** was defined as the time between the injection of anaesthetic solution and loss of sensation at the T6 dermatome. Sensory block was assessed by loss of cold touch along midclavicular line bilaterally using spirit cotton. This assessment started immediately after turning the patient to supine position and continued every minute till loss of sensation to cold touch at T6 level was noted. **Maximum level of sensory blockade and time taken for the same**: was defined as the time from the injection of the anaesthetic solution to the maximum level of sensory blockade attained. The **duration of sensory block** was defined as the time between the intrathecal administration of anaesthetic solution and two segment sensory regression.

Duration of two segment sensory regression: was defined as the time taken from the maximum level of sensory block attained till the sensation has regressed by Two segments.

Motor block

Motor block was assessed bilaterally using Modified Bromage scale.

Modified Bromage score[42]

0 - Able to move the hip, knee and ankle.

1 - Unable to move the hip, but able to move knee and ankle (onset).

2 - Unable to move the hip and knee, but able to move the ankle.

3 - Unable to move the hip, knee and ankle (maximum).

Assessment of motor block was started immediately after turning the patient to supine position and continued every minute till Bromage score of 3 was reached which defines **maximum motor block** and time to achieve it was noted. The **onset of motor block** was defined as the time to achieve Bromage score of 1 from the time of intrathecal injection.

Sedation

Ramsay sedation score[43] was used to assess the degree of sedation.

1. Anxious and Agitated.

2. Cooperative, oriented, tranquil

3. Responds only to verbal commands

4. Asleep with brisk response to light stimulation

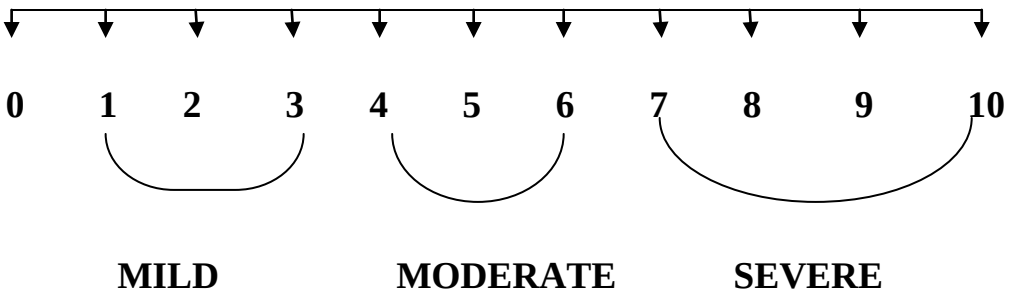
5. Asleep with sluggish response to light stimulation

6. Asleep without response to light stimulation

Time for recue analgesia

The time duration for rescue analgesia was defined as the period from spinal injection to the first occasion when the patient complaints of pain (VISUAL ANALOGUE SCALE – 3) in the postoperative period.

VAS SCORE



OBSERVATION AND ANALYSIS

All 60 patients with ASA physical status I/II who satisfied all inclusion criteria were randomly divided into two groups and underwent elective lower segment caesarean section under subarachnoid block in Raja Mirasudhar Hospital, attached to Thanjavur Medical College Thanjavur. All the patients completed the study without any exclusion.

The collected data were analyzed by t test and results obtained in form of mean and standard deviation. The probability value **p < 0.05** is considered as **statistically significant**. The results were as follows:

DEMOGRAPHIC DATA

Demographically all parturient were comparable with regards to age, height and weight.

Age distribution

Mean age in both groups were around 26. The p value for mean age was not stastitically significant (p value = 0.806)(tab1,fig 5)

Tab 1: Age distribution

	MEAN ± SD	p value < 0.05
GROUP A	26.03 ± 3.86	p = 0.806 Not Significant
GROUP B	26.27 ± 3.45	

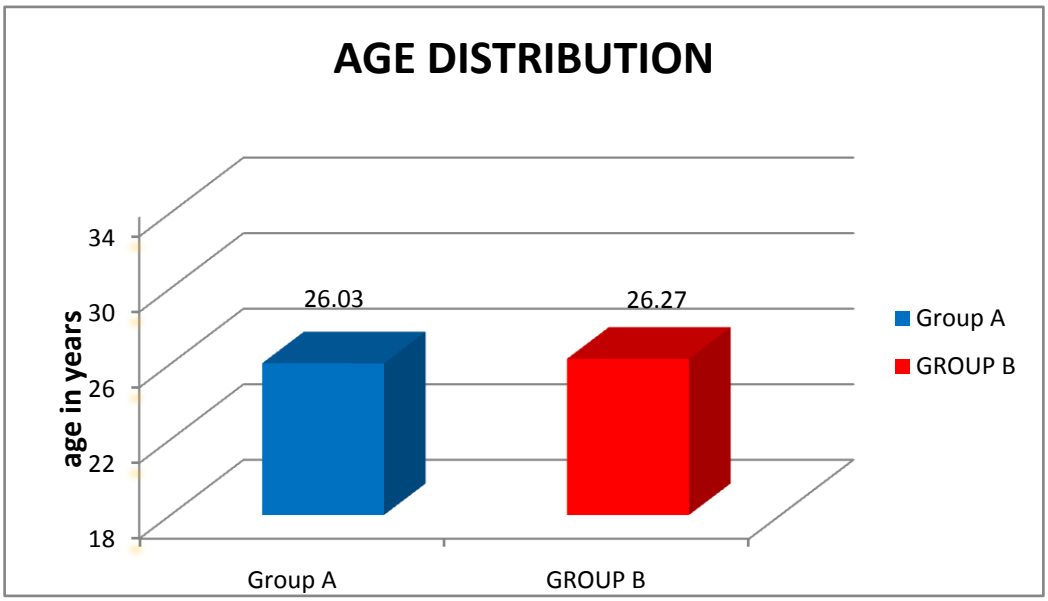


Fig 5

HEIGHT DISTRIBUTION

Mean height was Statstically not significant (p value = 0.212) (tab 2 and fig 6).

Tab 2: Height distribution

	MEAN ± SD	p value < 0.05
GROUP A	148.87 ± 5	p = 0.212 Not Significant
GROUP B	150.6 ± 5.62	

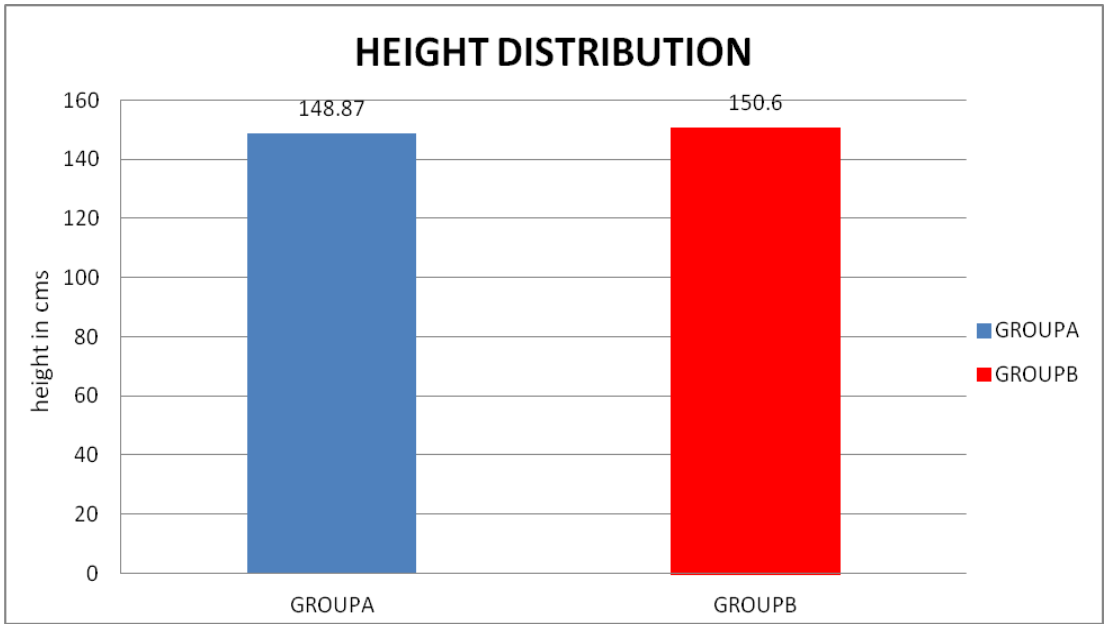


FIG 6

WEIGHT DISTRIBUTION

The mean weight distribution of two groups was statistically not significant.(tab3,fig 7)

Tab 3: Weight distribution

	MEAN ± SD	p value < 0.05
GROUP A	55.77 ± 7.468	p = 0.602 Not significant
GROUP B	56.83 ± 8.272	

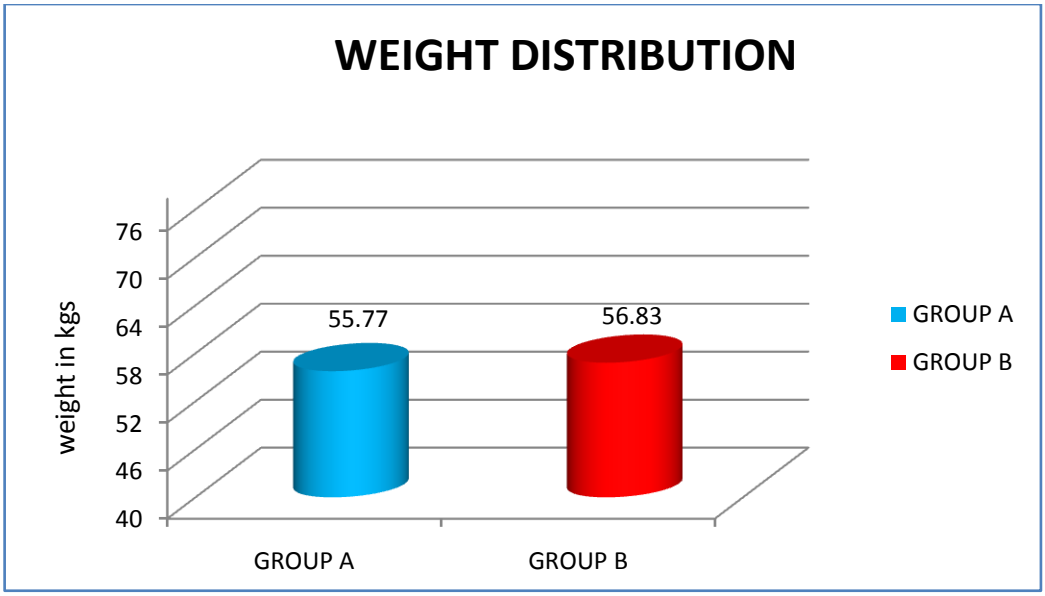


Fig 7

DURATION OF SURGERY

The mean duration of surgery in group A and group B were comparable without statistical significance. (Tab 4)

Tab 4: Mean duration of surgery

	MEAN ± SD	p value < 0.05
GROUP A	50 ± 9.826	p = 0.475 Not significant
GROUP B	51.67 ± 8.023	

COMPARISION OF EFFICACY OF TWO DRUGS

ONSET OF MOTOR BLOCKADE

Average time taken for onset of motor blockade was **faster** in group A than in group B (2.07 minutes Vs 2.57 minutes). It was found to be statistically significant (p value = 0.044) (tab 5, fig 8).

Tab 5: Onset of motor blockade

	MEAN ± SD	p value < 0.05
GROUP A	2.07 ± 0.91	p = 0.044 Significant
GROUP B	2.57 ± 0.97	

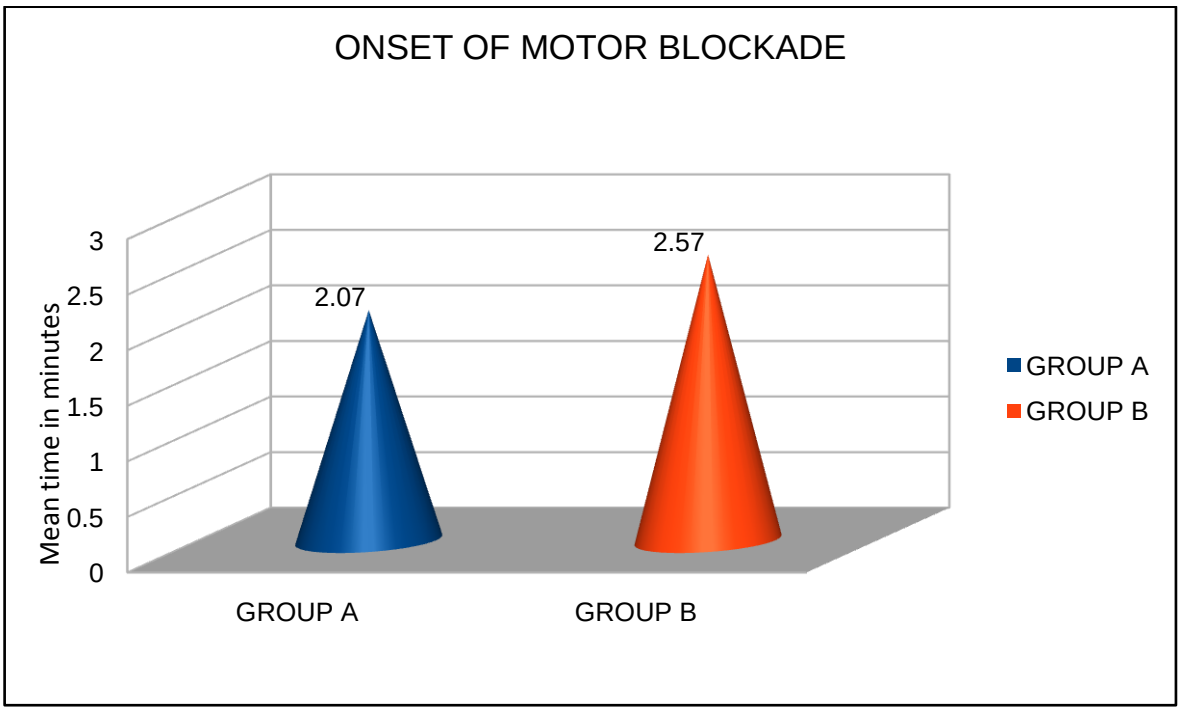


FIG 8

TIME FOR COMPLETE MOTOR BLOCKADE

Mean time for complete motor block of group A was 5.27 minutes & for group B was 6.10 minutes. It was not statistically significant (p = 0.073) (tab 6 and fig 9).

Tab 6: COMPLETE MOTOR BLOCKADE

	MEAN ± SD	p value < 0.05
GROUP A	5.27 ± 1.98	p = 0.073 Not Significant
GROUP B	6.10 ± 1.56	

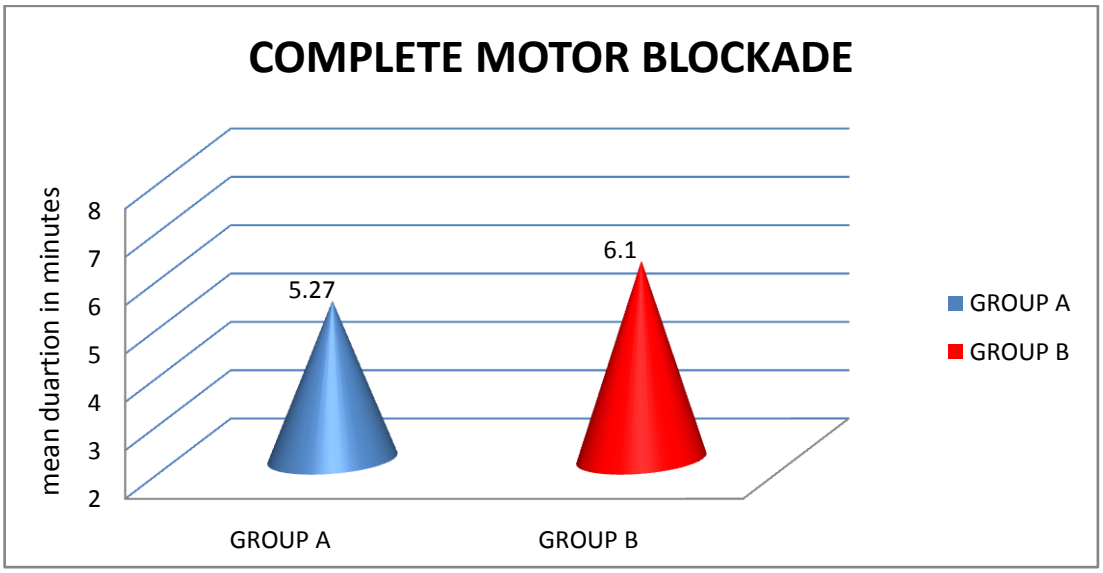


FIG 9

ONSET OF SENSORY BLOCKADE

The mean time for onset of sensory block for group A was 4.47 minutes & 4.67 minutes for group B which was not statistically significant (p value = 0.618) (tab 7 and fig10).

Tab 7: Onset of sensory blockade

	MEAN ± SD	p value < 0.05
GROUP A	4.47 ± 1.66	p = 0.618 Not Significant
GROUP B	4.67 ± 1.42	

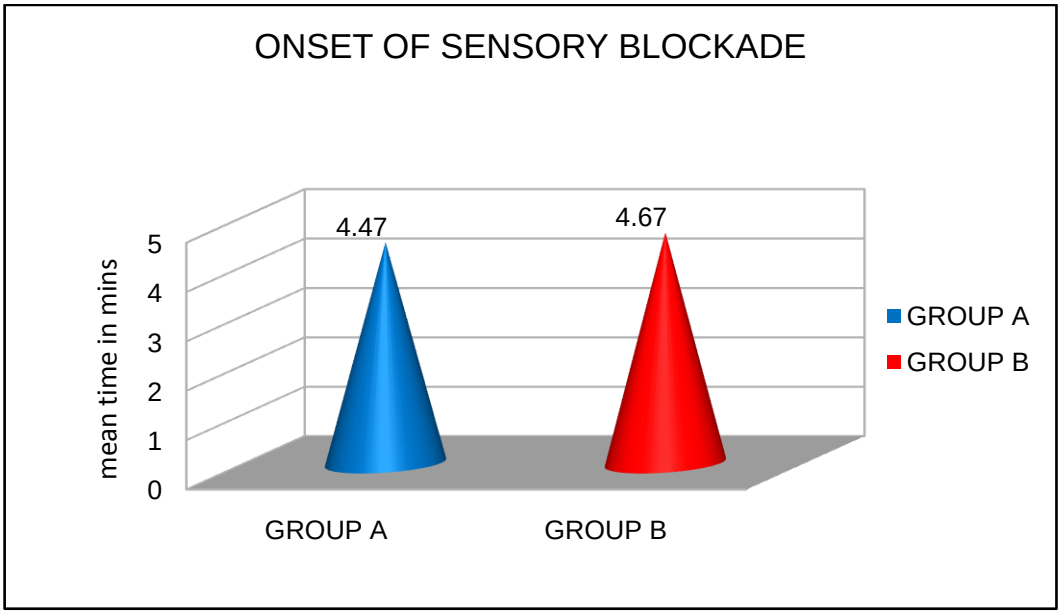


FIG 10

MAXIMUM LEVEL OF BLOCK

The median maximum level of sensory block was **T4** in both group **A** and group **B**. And the range in group **A** was from **T2 to T6** Vs group **B** ranging from **T2 to T4.**

TIME TO REACH MAXIMUM LEVEL OF SENSORY BLOCKADE

The mean time to reach maximum level of sensory block in group A was 12.70 minutes and 12.40 in group B which was not significant (p = 0.686)(tab 8 and fig 11).

Tab 8: Time for maximum sensory blockade

	MEAN ± SD(MEDIAN)	p value < 0.05
GROUP A	12.70 ± 2.84(T4)	p = 0.686 Not Significant
GROUP B	12.40 ± 2.88(T4)	

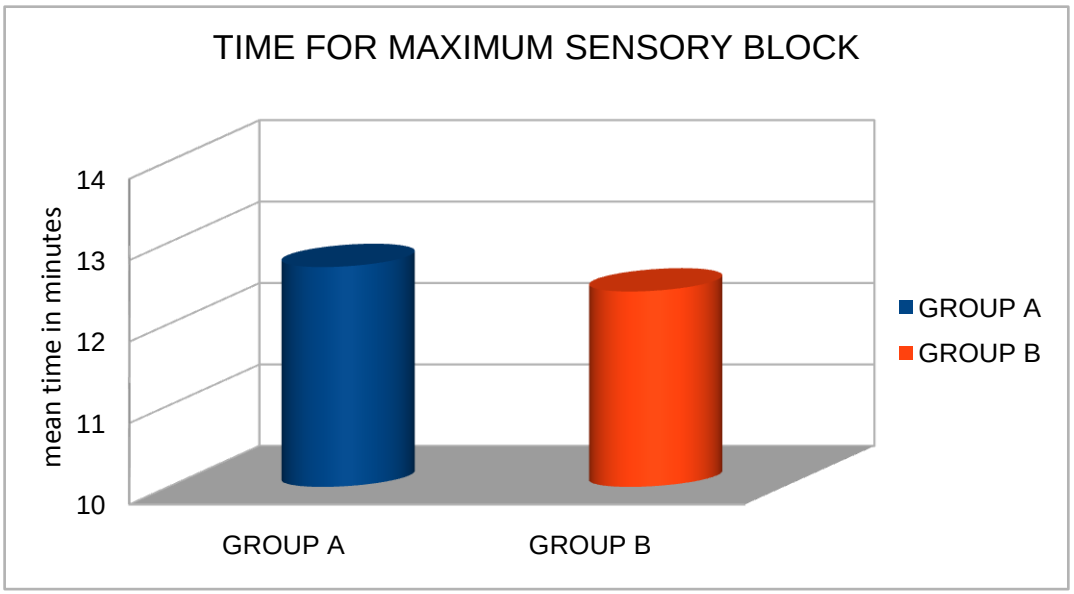


FIG 11

TIME FOR TWO SEGMENT REGRESSION

The mean two segment regression time was 93 minutes in group A and 88.33 minutes in group B was not statistically significant (tab 9 and fig12).

Tab 9: Two segment regression time

	MEAN ± SD	p value < 0.05
GROUP A	93 ± 12.91	p = 0.126 not significant
GROUP B	88.33 ± 10.2	

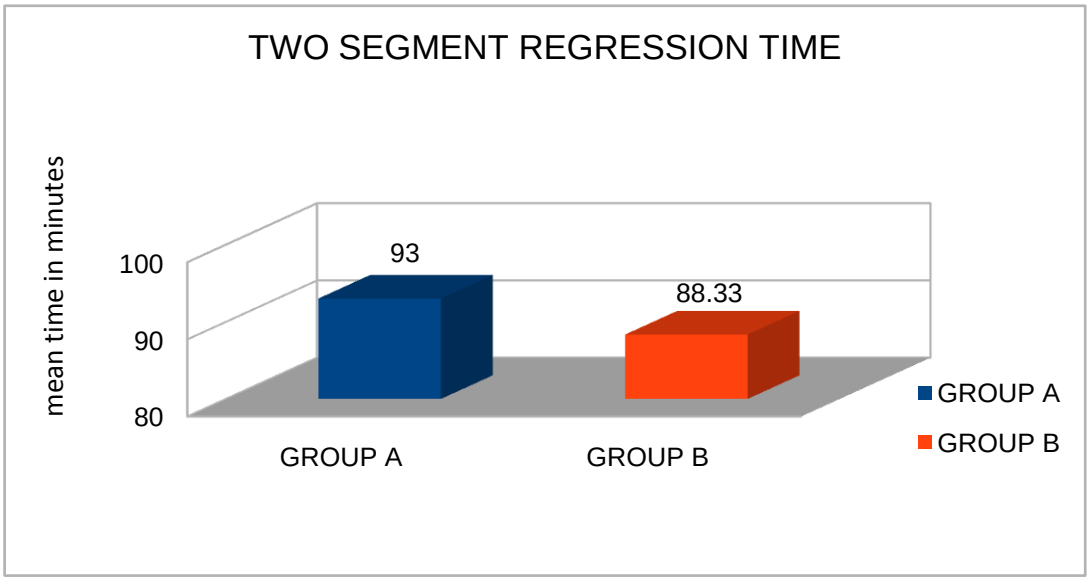


FIG 12

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COMPARISION OF SEDATION SCORE

The mean sedation score of Group A at the start of the surgery was higher than Group B (1.13 Vs 1) which was statistically significant (p = 0.039) and later on it was not statistically significant in the other intervals (tab 10 and fig 13).

Tab 10: Sedation score

TIME IN HR	GROUP A MEAN ± SD	GROUP B MEAN ± SD	p value < 0.05
First ½ HR	1.13 ± 0.346	1 ± 0	0.039 (Significant)
Second ½ HR	1.93 ± 0.365	1.97 ± 0.183	0.656
2 HR	2	2	-
6 HR	2	2	-

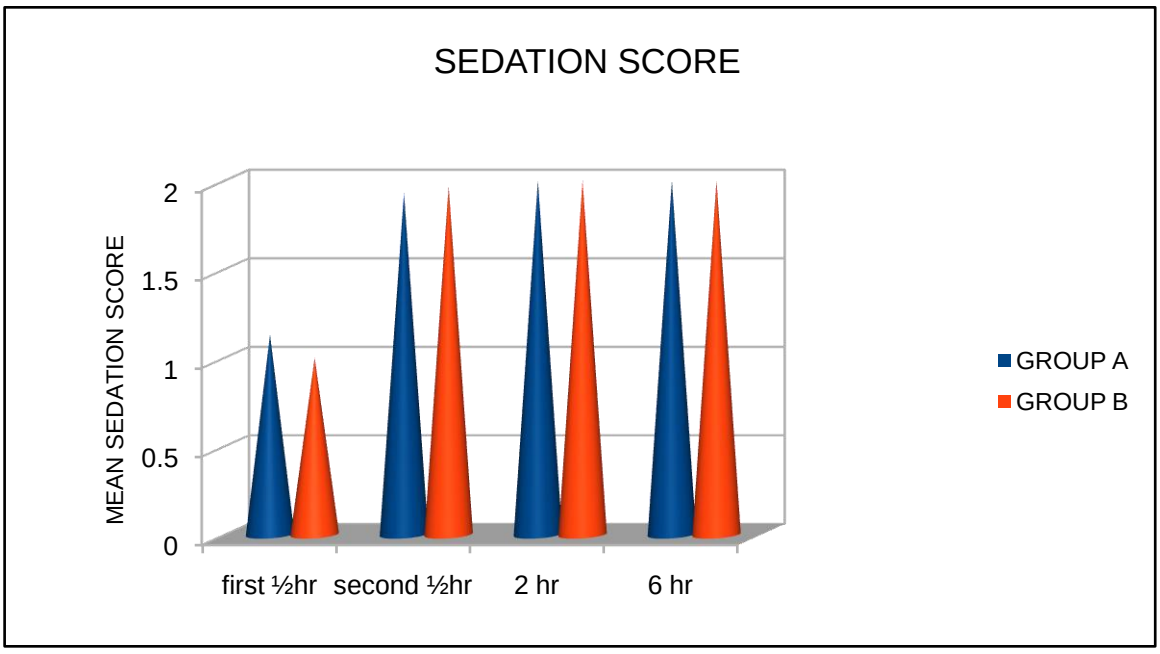

FIG 13

COMPARISION OF HEMODYNAMICS OF TWO GROUPS

COMPARION OF MEAN HEART RATE

The mean heart rate of Group B (p value = 0.022, 0.005, 0.003, 0.047) was significantly and continuously **lower** than group A in the first 12 minutes (3, 6, 9, 12 minute intervals). In the next three intervals the mean heart rate was stable and similar in both groups. (Tab 11, fig 14)

Tab 11: Mean heart rate

TIME IN MIN	GROUP A MEAN ± SD	GROUP B MEAN ± SD	p value < 0.05
O MIN	95.9 ± 11.74	94.73 ± 9.37	0.672
3 MIN	94.87 ± 15.58	87.27 ± 8.28	0.022 (significant)
6 MIN	88.6 ± 16.67	77.93 ± 10.84	0.005 (significant)
9 MIN	82.73 ± 12.14	74.47 ± 8.46	0.003(significant)
12 MIN	80.03 ± 11.31	74.27 ± 10.72	0.047(significant)
15 MIN	79.17 ± 13.49	78.13 ± 15.44	0.784
30 MIN	83.03 ± 14.40	81.47 ± 8.44	0.609
60 MIN	78.97 ± 10.1	77.4 ± 6.45	0.477

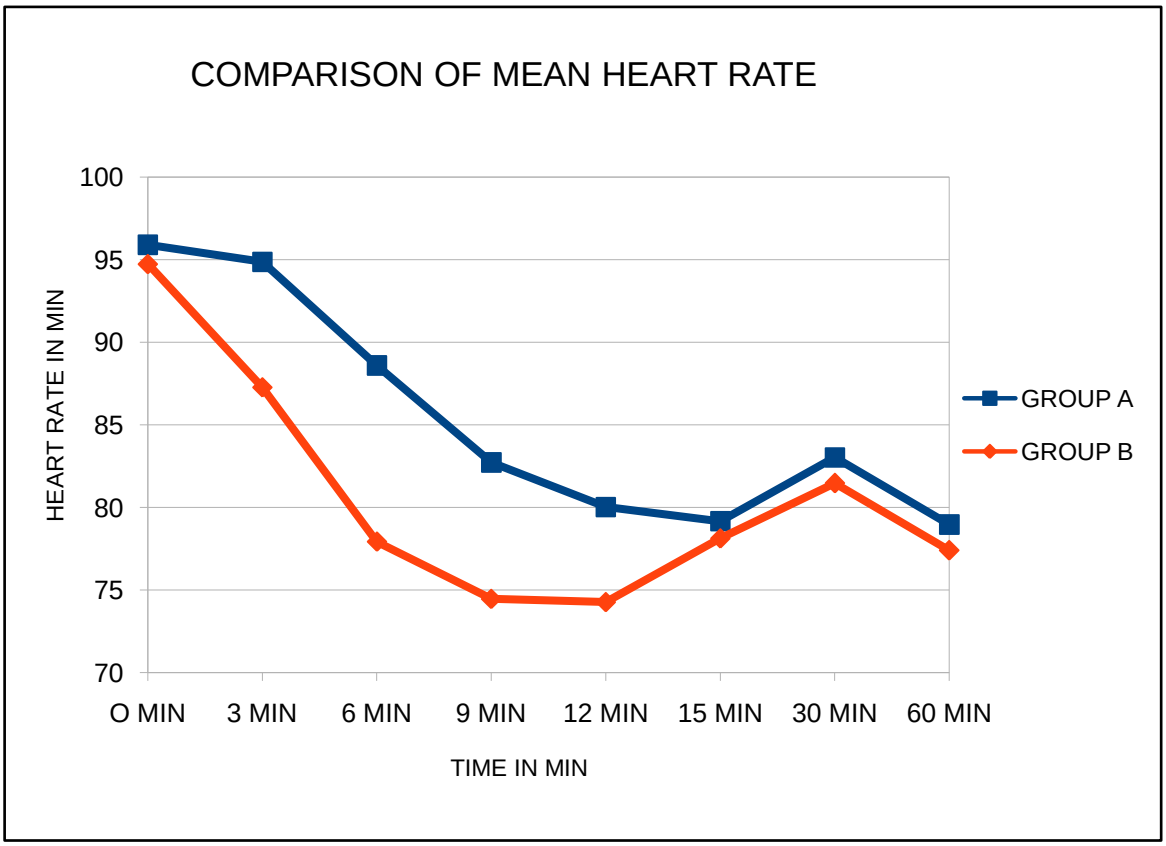

FIG 14

COMPARISION OF MEAN SYSTOLIC BLOOD PRESSURE

The mean systolic blood pressure of Group B was **lower** than Group A at three intervals (9min, 12 min & 30 min) which was found to be statistically significant 108.57 Vs 104.33, 107.2 Vs 101.4 and 105.2 Vs 98.4 respectively). Though the systolic BP was not significant at the 15th minute interval, it was higher in group B than group A (tab 12 and fig 15)

Tab 12: Mean systolic blood pressure

TIME IN MIN	GROUP A MEAN ± SD	GROUP B MEAN ± SD	p value < 0.05
O MIN	128.77 ± 10.28	132.93 ± 5.00	0.051
3 MIN	117.5 ± 10.55	118.87 ± 6.92	0.555
6 MIN	111.5 ± 9.18	109.13 ± 9.03	0.312
9 MIN	108.57 ± 5.48	104.33 ± 7.37	0.014(significant)
12 MIN	107.23 ± 8.04	101.47 ± 9.23	0.002 (significant)
15 MIN	105.9 ± 11.19	109.33 ± 9.25	0.201
30 MIN	105.2 ± 10.72	98.47 ± 8.73	0.010 (significant)
60 MIN	112.4 ± 6.10	108.53 ± 17.91	0.268

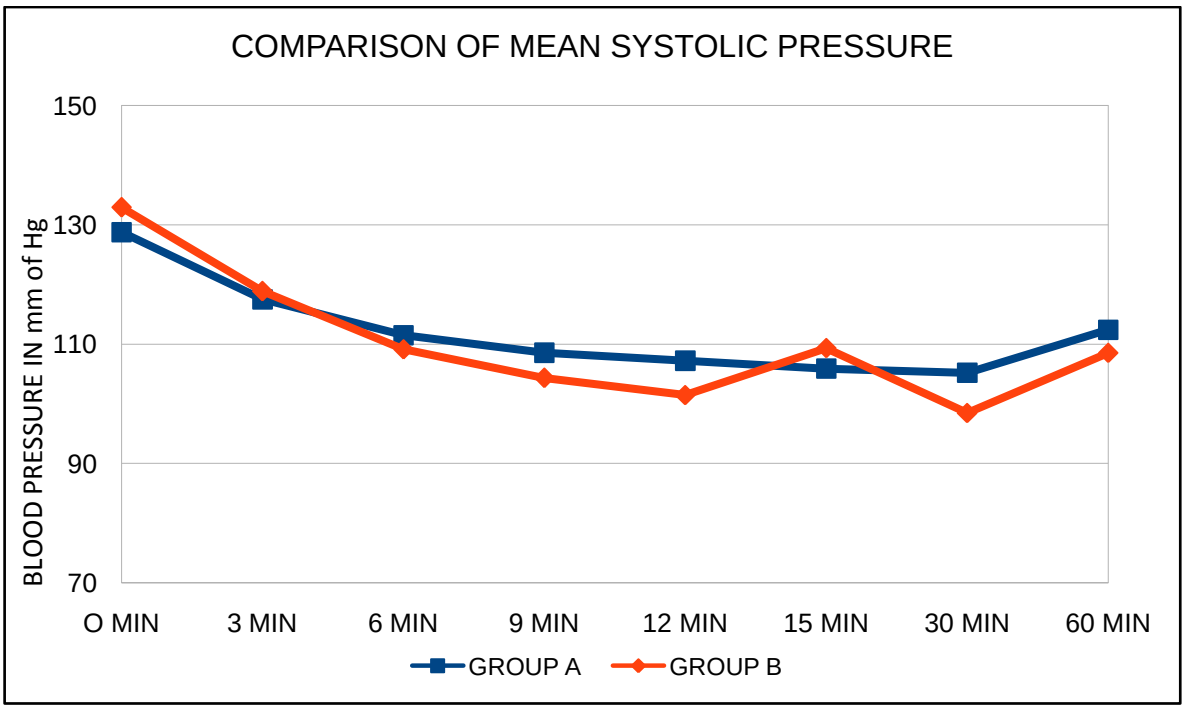

FIG 15

COMPARISION OF MEAN DIASTOLIC BLOOD PRESSURE

The mean diastolic blood pressure of Group A was **lower** than Group B at two intervals, 15 min (59.8 Vs 65.13) (p value 0.008) and 60 min (64.77 Vs 68) (p value 0.007) (tab 13 and fig 16).

Tab 11: Mean diastolic blood pressure

TIME IN MIN	GROUP A MEAN ± SD	GROUP B MEAN ± SD	p value < 0.05
O MIN	79.2 ± 94	82.13 ± 4.86	0.090
3 MIN	69.17 ± 10.88	71.8 ± 5.49	0.242
6 MIN	64.6 ± 8.23	64.6 ± 6.66	1
9 MIN	62.67 ± 5.15	61.53 ± 6.78	0.469
12 MIN	60.27 ± 6.02	58.77 ± 9.49	0.468
15 MIN	59.8 ± 7.17	65.13 ± 7.96	0.008 (significant)
30 MIN	58.63 ± 7.52	55.27 ± 6.77	0.074
60 MIN	64.77 ± 4.57	68 ± 4.29	0.007 (significant)

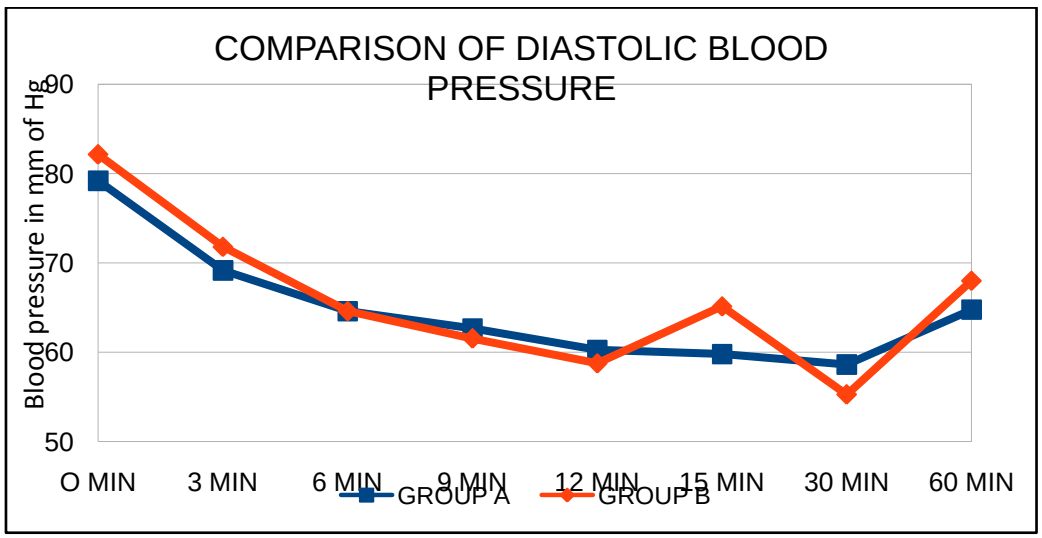

FIG 16

COMPARISION OF MEAN ARTERIAL PRESSURE

The mean arterial pressure of Group A compared to Group B was **higher** and statistically significant (p = 0.034) at 30 minutes interval (69.5 ± 6.90 Vs 65.8 ± 6.52) (tab 14 and fig 17).

Tab 14: Mean arterial blood pressure

TIME IN MIN	GROUP A MEAN ± SD	GROUP B MEAN ± SD	p value < 0.05
O MIN	91.5 ± 7.48	94.53 ± 4.86	0.068
3 MIN	81 ± 9.99	82.67 ± 5.76	0.432
6 MIN	76.73 ± 8.57	75.13 ± 7.15	0.436
9 MIN	73.43 ± 4.75	72.2 ± 7.34	0.471
12 MIN	71.67 ± 6.32	69.6 ± 9.29	0.317
15 MIN	71.3 ± 7.68	75.13 ± 8.97	0.081
30 MIN	69.57 ± 6.90	65.8 ± 6.52	0.034 (significant)
60 MIN	76.27 ± 4.89	77.73 ± 5.139	0.262

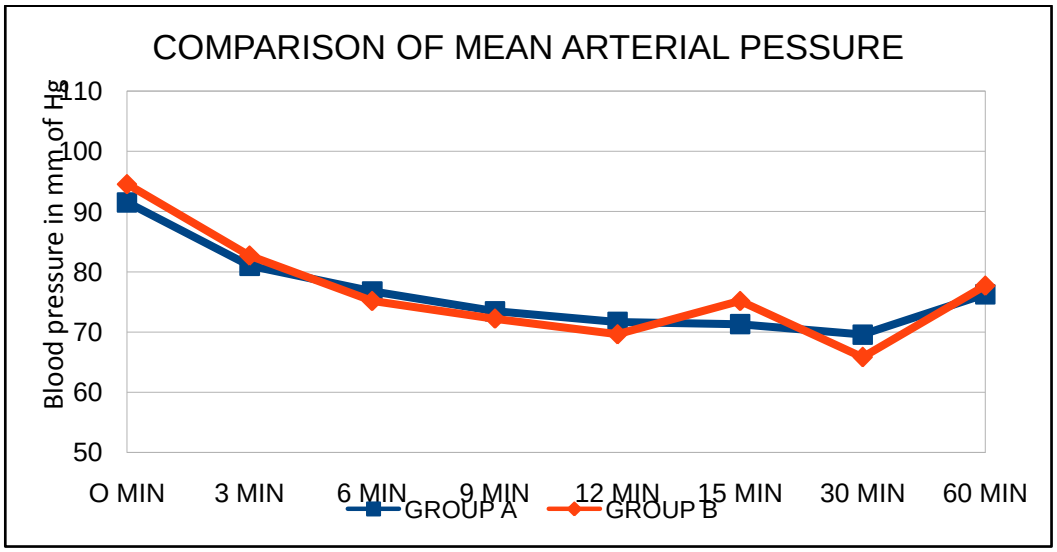

FIG 17

EPHEDRINE REQUIREMENT

The total **number** of patients requiring Ephedrine was **equal** in two groups (22 Vs 23) but the **mean ephedrine requirement** was **more** in group B (11.80 ± 4.38) than group A (9.50 ± 7.18) but was not statistically significant.(tab 15)

Tab 15: Mean Ephedrine Requirement

	MEAN ± SD	p value < 0.05
GROUP A	9.50 ± 7.18	p = 0.140 Not Significant
GROUP B	11.80 ± 4.38	

NEONATAL OUTCOME

COMPARISION OF APGAR AT 1 MINUTE

APGAR score at 1 minute compared between two Group A and B was not statistically significant (tab 16 and fig 18).

Tab 16: APGAR at 1 minute

	MEAN ± SD	p value < 0.05
GROUP A	7.93 ± 1.01	p = 0.658 Not Significant
GROUP B	7.83 ± 0.69	

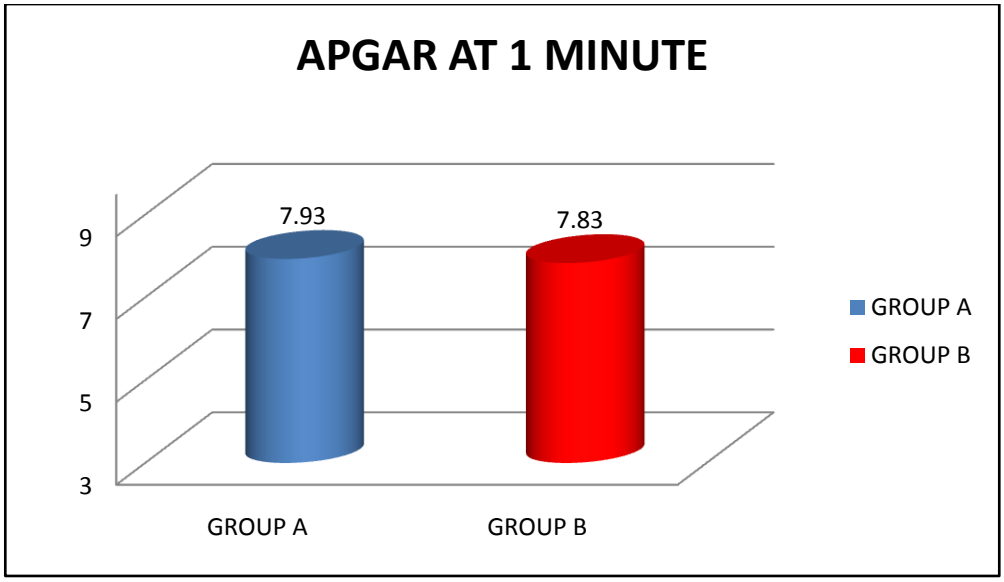

FIG 18

COMPARISION OF APGAR AT 5 MINUTE

APGAR score at 5 minutes compared between Group A and Group B was not statistically significant (9.40 Vs 9.87) (p value 0.078)(tab 17, fig 19).

Tab 17: APGAR at 5 minute

	MEAN ± SD	p value < 0.05
GROUP A	9.40 ± 0.49	p = 0.078 not significant
GROUP B	9.87 ± 0.35	

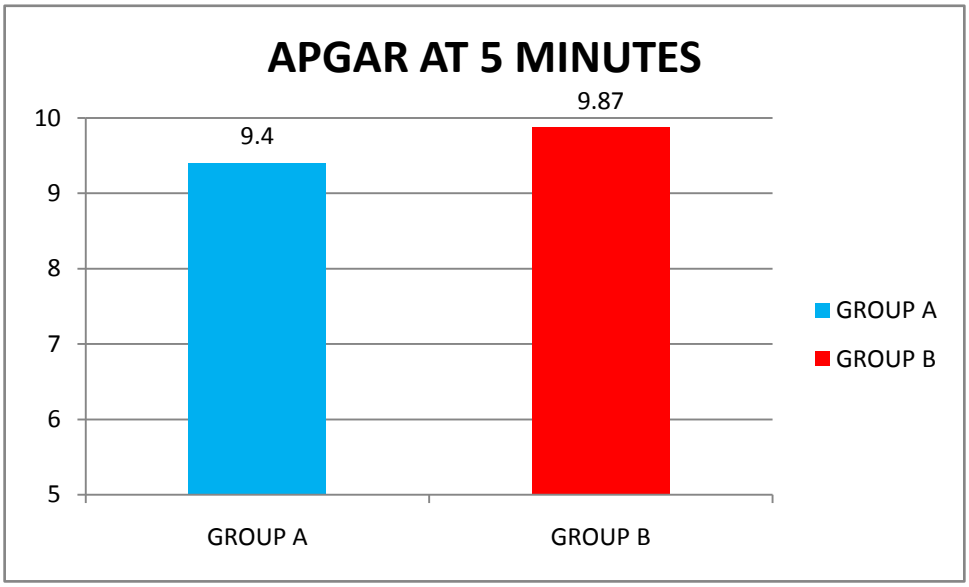

FIG 19

DURATION FOR RESCUE ANALGESIA

The duration for rescue analgesia was defined as the period from spinal injection to the first occasion when the patient complaints of pain (VAS >3) in the postoperative period. This was highly **prolonged** in Group A than Group B (232 Vs 151.5 minutes) and showed statistically significance (p value 0.000) (tab 18 and fig 20).

Tab 18: Time for rescue analgesia

	MEAN ± SD	p value < 0.05
GROUP A	232 ± 29.40	p = 0.00001 Significant
GROUP B	151.5 ± 19.44	

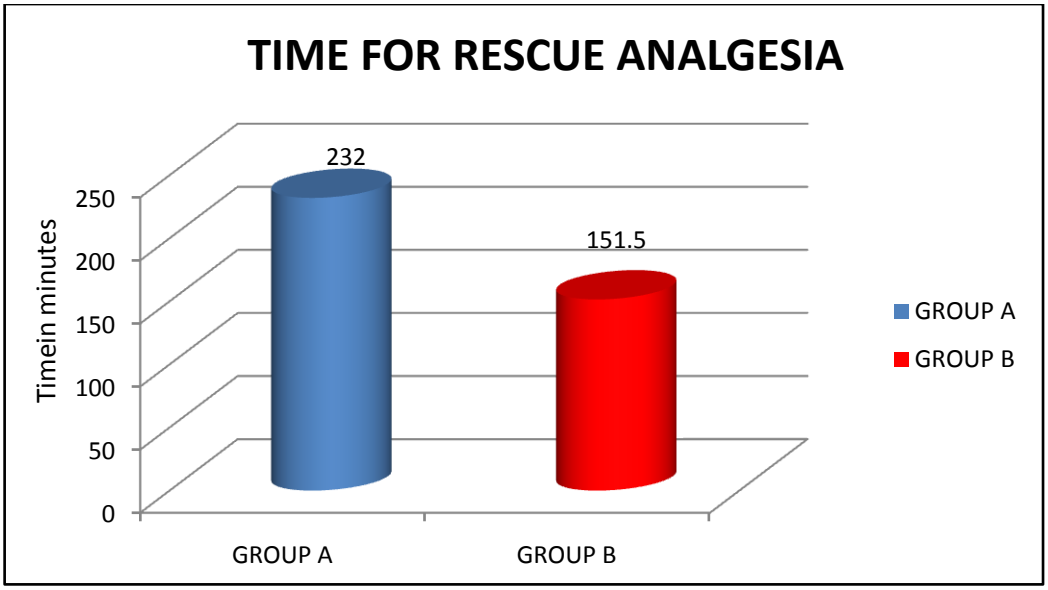

FIG 20

COMPARISION OF SIDE EFFECTS

The side effects such as nausea and vomiting were comparable in Group A and Group B, but Pruritis occurring in Group B was **64%** (19 out of 30 parturient) and there were no case reported in Group A so it was very highly significant in Group B (tab 19)

Tab 19: Side effects

SIDE EFFECTS	GROUP A MEAN ± SD	GROUP B MEAN ± SD	$p < 0.005$
NAUSEA	1.50 ± 0.51	1.53 ± 0.51	0.80
VOMITING	1.80 ± 0.41	1.73 ± 0.45	0.549
PRURITIS	0	1.33 ± 0.48	0.04 (Significant)

DISCUSSION

This prospective, randomized, double blinded study was conducted in Raja Mirasudhar Hospital attached to Thanjavur Medical College, Thanjavur with an aim to compare the effects of intrathecal Dexmedetomidine and Fentanyl as an adjuvant to 0.5% hyperbaric bupivacaine in caesarean section.

60 parturients belonging to ASA I and II undergoing caesarean section for non urgent obstetric indications under spinal anaesthesia completed this study.

Bupivacaine dosage

In this study 1.5 ml of 0.5% hyperbaric bupivacaine was used in both groups. **S Kiran et al**[34] conducted a double-blind comparison of three doses 7.5 mg, 8.75 mg and 10 mg (group A, B &C respectively) of 0.5% hyperbaric bupivacaine in 60 women undergoing elective caesarean under spinal anaesthesia. The incidence of hypotension was greater in groups B and C than in group A ($P \leq 0.05$). They observed 7.5-mg dose of 0.5% hyperbaric bupivacaine provided acceptable analgesia without any significant incidence of adverse effects such as maternal hypotension or bradycardia.

Based on **S Kiran et al**[34], in this study 7.5 mg (1.5ml) of 0.5% hyperbaric bupivacaine was used. Also **Mahdy et al**[35] conducted study in spinal anaesthesia in caesarean section on 90 parturient and used 10mg

(2ml) of 0.5% hyperbaric bupivacaine to which they added 0.5 ml of adjuvant. In this institute 7.5mg-10mg of hyperbaric bupivacaine without addition of adjuvant, based on height has been routinely used. As this study was planned for adding adjuvant to bupivacaine and to compare their efficacy it was decided to have 7.5mg as bupivacaine dosage.

Adjuvants and their dosage

Though there are many adjuvants used intrathecally in caesarean sections very few studies[35] have been conducted in comparing dexmedetomidine and fentanyl as adjuvant to hyperbaric bupivacaine. With an intention to compare these two adjuvants this study was conducted.

Biswas et al[6] suggested that there is a potential synergism between fentanyl and bupivacaine, fentanyl being a effective adjuvant to hyperbaric bupivacaine for caesarean section which have also been proved by various studies[46, 47,] Although intrathecal fentanyl has an excellent intra and post operative anaesthetic profile it has few adverse effects of which pruritis, was considered in higher incidence as suggested by **Herman et al**[48] and **Hunt et al**[8].

Gertler et al[49] have shown that dexmedetomidine is 8 times more potent than clonidine for α2 adrenoceptor [50]. The mechanism of prolongation of sensory and motor blockade is not yet clearly known.

Eisenach et al[51] has suggested that it may be due to inhibition of release of neuro transmitters of C- fibers and hyper polarization of post synaptic dorsal horn cells.

Even though they are pharmacologically different drugs, their effects on hemodynamic stability and intra operative analgesia as adjuvants are better than control group as shown by **Mahdy et al**[35]. Still these drugs differ in onset and duration of sensory and motor blockade[35, 14] and adverse effects[40, 37].

There have been various studies using fentanyl with dose of 25 µgm as adjuvant to hyperbaric bupivacaine intrathecally for caesarean section[52, 11, 57.

Kanazi GE et al[60] have used 3 µg dexmedetomidine in their study and said to have equipotent effect with clonidine. Many studies have chosen 5µg of dexmedetomidine as an additive to intrathecal hyperbaric bupivacaine and have proved its efficacy[40]. **Mahdy et al**[35]conducted a study using dexmedetomidine 5µgm as adjuvant to intrathecal hyperbaric bupivacaine in one of the group who had undergone caesarean section.

Hence in this study 5µgm dexmedetomidine and 25µgm fentanyl was chosen as an additive to hyperbaric bupivacaine.

Comparison of drug efficacy

Motor onset and time to maximum motor blockade

Mahdy et al[35] and **Al-Ghanem et al**[9]defined the onset of motor blockade as Bromage scale 3 (unable to move hip, knee and ankle). But ***this study*** defined the ***onset of motor blockade*** as Bromage scale 1 (unable to move hip but able to move knee and ankle). The time for maximum motor blockade (Bromage scale 3) in this study (equal to onset of their study) was found to be statistically insignificant (p value 0.073).

In this study the onset of motor blockade (Bromage 1) showed statistically significant (2.07 ± 0.90 Vs 2.57 ± 0.97, p value 0.044). But the onset of motor blockade in **Mahdy et al**[35] and **Al-Ghanem et al**[9] was not significant. This could be explained by their definition for the onset as Bromage scale 3.

It was found that dexmedetomidine acts faster than fentanyl whether the Bromage scale was **1**[this study] (2.07 ± 0.90 Vs 2.57 ± 0.97, p value = 0.044*****) or Bromage scale was **3**[**Mahdy et al**[35]] (4.7 ± 2.1 Vs 5.5 ± 2.43, p value = 0.17). Also **Mahdy et al**[35] found Dxm group had a prolonged motor **recovery** time compared to Fent group (176.2 ± 9.4 Vs 169.3 ± 9.1, p value 0.005). Similar finding was seen in many studies[60, 9]. Also **Vidhi Mahendru et al**[39] in their conclusion suggested that prolonged duration of motor blockade with dexmedetomidine may be undesirable for short term surgical procedures or ambulatory surgeries. Their study was conducted in lower

limb surgeries. In general caesarean section could be considered as short term surgical procedure and mostly done under spinal anaesthesia that restricts the early mobility in view of post dural puncture headache.

Sensory onset

In this study cold swab along midclavicular line bilaterally was used similar to **Mahdy et al**[35] and **Al-Ghanem et al**[9] to assess the sensory level, where as **Gupta R et al**[14] used pinprick (23G hypodermic needle) which would cause capillary bleeding and pain to parturient.

T6 level was taken as onset of sensory blockade in this study. **Srivatsava et al**[52], who had conducted the study using hyperbaric or isobaric bupivacaine (10mg) with fentanyl 25µg as adjuvant in caesarean section also used T6 dermatome level as onset of sensory blockade.

In this study onset of sensory blockade was not statistically significant (4.4 ± 1.65 Vs 4.67 ± 1.42, p value = 0.618), which was similar to **Mahdy et al**[35] (2 ± 0.74 Vs 2.1 ± 0.76, p value = 0.6).

Maximum sensory blockade

Maximum level of sensory blockade was T4 (median) in both groups (group A T2 – T6 and Group B T2 – T4). The mean duration to achieve this level was 12.70 ± 2.84 and 12.40 ± 2.88 in group A and group B respectively which was not statistically significant (p = 0.686). **Gupta R et al**[14] showed that a highest sensory block level of T5 (T4 – T8) in group D

and T6 (T4-T7) in group F and the time taken from injection to highest sensory level was 12.3 ± 1.8 Vs 12.1 ± 1.7 (p >0.05). Though the duration was similar and insignificant in both studies, Gupta **R et al**[14] used 12.5 mg of hyperbaric bupivacaine in lower abdominal surgeries whereas 7.5 mg of hyperbaric bupivacaine was used in caesarean sections in this study. Similar result was reported in study conducted by **Al- Ghanem et al**[9] on gynecological procedures. **Mahdy et al**[35] has not mentioned about the peak sensory blockade level.

In contrast, **Hem anand nayagam et al**[40] who had used similar adjuvant dosages (dexmedetomidine 5 µgm and fentanyl 25 µgm) to hyperbaric bupivacaine in randomized controlled study for lower abdominal surgeries showed statistically significance in both peak sensory blockade level (T 4 – T10 in group D, T 6 – T 10 in group F, p value 0.000) and time to reach peak sensory block (group D Vs group F, 12.92 ± 3.131 Vs 11.88 ± 2.156, p value < 0.05). This was explained by them as the solution with dexmedetomidine which was denser, caused the increased level of blockade in that group as compared with fentanyl group.

The dexmedetomidine group in this study and in **Hem anand nayagam et al**[40] had a similar duration to attain peak sensory block (12.70 ± 2.89 and 12.92 ± 3.131). Although there was concentration variation (0.375% and 0.25%) and volume variation (2ml and 1.6ml) of bupivacaine between this study and their study, the similarity to achieve peak sensory

blockade level of T4 and the duration to attain the same were probably because of the denser quality of dexmedetomidine as explained by **Kim SY et al**[61] and **Hem anand nayagam et al**[40]**.**

Two segment regression time

In this study time to two segment regression was 93 ± 12 Vs 88 ± 10 in group A and B respectively (p value 0.126). **Hem anand nayagam et al**[40] conducted a study using low dose intrathecal bupivacaine in lower abdominal surgeries and showed that time to two segment regression (mean TTSR) was not significant statistically (group D Vs group F = 61.79 Vs 60.24 minutes). In contrast, **Mahdy et al**[35] showed that time to two segment regression was 115 ± 7.6 Vs 107 ± 6.9 for Dxm and Fent group respectively and was statistically significant (p3 = 0.000). **Gupta R et al**[14]**,** observed similar results, 120 ± 22.2 (group D) Vs 76 ± 20.3 (group F) and was statistically significant (p = 0.001). In all the four studies the dosage of dexmedetomidine and fentanyl was the same. **Mahdy et al**[35] and this study included patients for caesarean sections, whereas **Gupta R et al**[14] and **Hem anand nayagam et al**[40] included patients for lower abdominal surgeries. A statistically significant prolongation of two segment regression in **Mahdy et al**[35] and **Gupta R et al**[14] could be explained by the higher dosage of bupivacaine (10mg and 12.5mg) compared to 7.5 mg and 4mg in **this study** and **hem anand nayagam et al**[40] respectively.

The significant prolongation of motor blockade in dexmedetomidine group was found to be associated with higher dosage of bupivacaine.

Sedation score

In this study Ramsay sedation score has been instituted to compare the sedation level of the parturient in two groups. It was observed to be statistically significant in first ½ hr (1.13 ± 3.46 Vs 1.00 ± 0.00, p value < 0.03). **Mahdy et al**[35] has also observed that the mean sedation score was higher for Dxm group compared to Fent group (3.2 ± 0.5 Vs 2.2 ± 0.23, p value 0.00) similar to this study. Also **Gupta R et al**[14] had a mean sedation score more for group D (3.8 ± 0.5 Vs 2.2 ± 0.13, p value < 0.05). **Kanazi et al**[60] who used smaller intrathecal dose (3µgm) of dexmedetomidine with bupivacaine showed that there was lack of sedation. This could be explained by the dosage difference (3µgm Vs 5µgm) and the patient profile (male gender, old age).

Comparison of Hemodynamics

Heart rate

Mahdy et al[35] conducted a study comparing dexmedetomidine and fentanyl as adjuvants in caesarean section and had no significant difference in mean heart rate. In our study mean heart rate of group B was significantly

and continuously lower in initial 4 successive intervals (3, 6, 9and 12 minutes).This could be expressed by two reasons, a delay in fall in heart rate in group A or by a steady fall in heart rate in group B.

The delay in fall in heart rate in group A could be due to the **lower dosage** (5 µgm) being supported by **Kanazi et al**[60] (3 µgm). **Anjan das et al**[53] who compared the effect of two different dosage of dexmedetomidine 5µgm (D5) & 10µgm (D10) as adjuvant to intrathecal bupivacaine for abdominal hysterectomy, also observed greater number of patients developed bradycardia in D 10 group (14 patients) who required atropine, compared to D 5 group (5 patients).

The reason for steady fall of heart rate in group B could be due to dose dependent depression of carotid sinus baroreceptor. Fentanyl has vagal nucleus stimulation action which produces significant fall in heart rate, supported by various studies[38, 6, 57]. All though fall in heart rate was significant in fentanyl group, only one patient required inj.atropine 0.6 mg IV as supplementation.

Blood pressure

The fall in systolic blood pressure in group B was more compared to group A particularly in initial 3 intervals (9, 12 minute & 30 minute) in this study. This was statistically significant [108 ± 5.48 Vs 104 ± 7.37 (p value 0.014), 107.23 ± 8.04 Vs 101.47 ± 9.23(p value 0.002) and 105.2 ± 10.72 Vs 98.4 ± 8.73 (p value 0.001)]. There was gradual fall in diastolic blood

pressure in group A which was statistically significant later in the study (15 & 60 minutes after spinal anaesthesia). (59.8 ± 7.17 Vs 65.13 ± 7.96 (p value 0.008) & 64.77 ± 4.57 Vs 68 ± 4.29 (p value 0.007)

The variation in mean arterial blood pressure in this study did not have significant difference between two groups except for fall in group B at 30 minute (69.57 ± 6.9 Vs 65.8 ± 6.52) compared to group A which was statistically significant (p = 0.034).

Sheriff A Abdelhamid et al[54] in their study to evaluate the role of dexmedetomidine added to heavy bupivacaine intrathecally for lower abdominal surgeries had observed that dexmedetomidine evokes a biphasic blood pressure response, a short hypertensive phase and a subsequent hypotensive phase. The two phases are mediated by α2B-AR and α2A-AR receptors respectively. Initial hypertensive phase lasts for 5 to 10 minutes followed by fall in blood pressure about 10 to 20 % below baseline which was caused by inhibition of central sympathetic outflow. This could explain the initial less fall of blood pressure and later stabilization of the same in group A compared to group B in this study.

Uma Srivatsava et al[52] conducted a study comparing hyperbaric or plain bupivacaine (10mg) with intrathecal fentanyl (25µgm) during caesarean section and found that the lower systolic blood pressure in the hyperbaric group. **Al-Ghanem et al[9]** has observed that hypotension was more in fentanyl group than dexmedetomidine group but did not reach a

significant difference and the hypotension also occurred around 25 to 30 minutes after spinal anaesthesia similar to the observation in this study. The rise in blood pressure group B at 15th minute interval could be explained by the administration of ephedrine in the previous 9th and 12th minute intervals to treat the hypotension. This was observed by the larger ephedrine dosage required in the group B (11.80 ± 4.38 Vs 9.50 ± 7.18, p value 0.140).

Comparison of APGAR Score

The neonatal outcome in this study was assessed by APGAR score during first minute and fifth minute after delivery of the baby. It was found to be statistically insignificant (7.93 Vs 7.90, p value = 0.658 for 1st minute, 9.40 Vs 9.87, p value = 0.07 for 5th minute) which was comparable with **Mahdy et al**[35]. **Abady A Mohamed et al**[55] who compared the effect of intrathecal dexmedetomidine (10 µgm) and fentanyl (20 µgm) in labor analgesia has shown that neonatal outcome based on APGAR had no significant difference between the two groups similar to this study even though the dose of dexmedetomidine was higher in their study.

Although there is uteroplacental transfer of dexmedetomidine it does not affect the fetal well being which has also been proven by **S Fyneface-Ogan et al**[38] who studied comparative effect of single short intrathecal bupivacaine with dexmedetomidine (2.5µgm) and fentanyl (25 µgm) on

labor outcome. They found the APGAR score did not show significant difference. In this study even though the dexmedetomidine dose (5 µgm) was higher compared with **S Fyneface-Ogan et al[38]** study the neonatal outcome was not affected.

Rescue analgesia

The duration for request of rescue analgesia was significantly prolonged in group A compared with group B (232 ± 29.40 Vs 151.5 ± 19.44, p value = 0.00). Patients in group A had a longer duration of analgesia by 53% compared to group B. This would be a definitely excellent property of dexmedetomidine comparing to fentanyl. **Gupta R et al[14]** who conducted a study in lower abdominal surgeries with intrathecal bupivacaine (3.5ml) along with same dosage of adjuvants has observed 49% longer duration of post operative analgesia in group D compared to group F.

Neuraxial administration of dexmedetomidine produces dose dependent prolongation of sensory block, increase in motor block, along with prolongation of post operative analgesia by acting on spinal dorsal horn α2-AR receptors (**Panzer O et al**[56]). The antinociceptive effect of adding dexmedetomidine to bupivacaine intrathecally acts by depressing the release of neurotransmitters of C-fibers and by hyper polarization of postsynaptic dorsal horn neurons (**Joana Afonso et al[32], Anjan et al[53]**). Synergistic mechanism along with bupivacaine was said to produce prolonged sensory duration of blockade and a delay for request of rescue analgesia.

Whereas intrathecal fentanyl which is a lipophilic Opioid agonist, exerts its effects by combining with μ receptors in dorsal horn of spinal cord and may have supraspinal spread and action also[40, 9]. **Seewal et al[58]** studied different doses of fentanyl added to intrathecal bupivacaine in lower abdominal surgeries and shown fentanyl was not causing dose dependent prolongation of analgesia when it was more than 10 μgm.

Adverse effects

In this study there were few adverse effects such as nausea, vomiting and pruritis. Nausea (1.50 ± 0.51 Vs 1.53 ± 0.51, p value 0.80) and vomiting (1.80 ± 0.41 Vs 1.73 ± 0.45, p value 0.549) were found to be statistically insignificant similar to **Mahdy et al[35]** (p = 0.63) and **Gupta R et al[14]** (p value > 0.05).

Pruritis occurring with usage of fentanyl has been observed in various studies[14, 35]. In this study also pruritis occurrence was observed to be very high in group B. It was 64 % in group B (19 out of 30 parturient) whereas there were no pruritis was encountered in group A which was found to be highly significant statistically. **Dilesh et al[59]** who conducted a study in labor analgesia comparing intrathecal dexmedetomidine versus fentanyl with bupivacaine also showed 50% of the patients in fentanyl group experienced pruritis.

Ephedrine requirement

Although the number of patients requiring ephedrine in group A (n = 22) and group B (n = 23) was nearly equal, the mean dose requirement was lower in group A (9.5 ± 7.18) compared to group B (11.8 ± 4.38), but the requirement dose was not significant statistically. **Al-Ghanem et al[9]** who studied the effect of dexmedetomidine and fentanyl as adjuvant to intrathecal bupivacaine also observed that ephedrine requirement was higher in fentanyl group, but was not statistically significant.

In this study sitting position was employed to perform spinal anaesthesia. **Inglis et al[62]** who had demonstrated that when 2.5ml of hyperbaric bupivacaine was used for single shot spinal anaesthesia for caesarean section the ephedrine requirement (sitting Vs lateral, 10.5 ± 6.2 Vs 13.5 ± 12.24) was found to be higher in lateral position. This could explain the reduced requirement of ephedrine in this study.

LIMITATIONS

Motor recovery to Bromage scale 0, Sensory regression time to S1 segment, umbilical artery sampling for acid base analysis and total post operative analgesic requirement were not noted in this study. A placebo group with low dose bupivacaine (7.5mg) alone would have been a better comparison for either of the adjuvant group.

Kiran S et al[34] conducted a double blinded study in women undergoing elective caesarean section under spinal anaesthesia comparing three different doses (7.5mg, 8.75mg and 10mg) of 0.5% hyperbaric bupivacaine ***without adjuvants*** and observed that 7.5mg dose group provided acceptable analgesia without any significant incidence of adverse effects such as maternal hypotension or bradycardia.

SUMMARY

This clinical study was aimed with an intention to compare the effects of intrathecal dexmedetomidine and fentanyl as adjuvant to 0.5% hyperbaric bupivacaine for spinal anaesthesia in caesarean section. This prospective randomized double blinded study was conducted on 60 parturients of ASA physical status I and II in the age group 18 to 35 years, posted for elective lower segment section at Raja Mirasudhar Hospital attached to Thanjavur Medical College, Thanjavur from period of June 2014- July 2015.

Parturients were randomly allocated into two groups, Group A receiving 5µg dexmedetomidine (0.5ml) and Group B receiving 25µg fentanyl (0.5ml) with 0.5% hyperbaric bupivacaine 7.5mg (1.5ml) intrathecally.

Hemodynamic monitoring including heart rate, blood pressure and oxygen saturation were recorded at 0, 3, 6, 9, 12, 15 minute and there after every 15 minute interval was recorded up to 60 minutes.

The onset and duration of motor and sensory blockade, time to two segment regression, degree of sedation, hemodynamic changes, APGAR score, side effects and time for first rescue analgesia were observed.

The data collected were analyzed statistically with appropriate tests.

Demographically the two groups were comparable. The *onset of motor blockade* was found to be **significantly shorter** in dexmedetomidine

group than fentanyl group. The onset and duration of sensory block and the time to two segment regression were not statistically significant.

The time for first post operative rescue analgesia was **significantly prolonged** in dexmedetomidine group than fentanyl group. Similar results were obtained by **Gupta R et al[14]**. The degree of **sedation was higher** in dexmedetomidine group during the initial period of study similar to **Mahdy et al[35].** Hemodynamically dexmedetomidine group was found to be more stable because of its biphasic effect. The fall in blood pressure caused by fentanyl required treatment with ephedrine more often than dexmedetomidine group. The heart rate was significantly lower in fentanyl group but there was no documented bradycardia in either group.

Pruritis occurrence was **very highly significant** in fentanyl group about **64%** (19 patients) compared to dexmedetomidine group (0) similar to **Dilesh et al[59]**. Neonatal outcome was not affected in both the groups.

CONCLUSION

This study concluded that on comparing the effect of adding dexmedetomidine and fentanyl to hyperbaric bupivacaine in spinal anaesthesia for elective caesarean section showed dexmedetomidine received parturients had:

1. The onset of motor blockade significantly faster.
2. Sedation significantly higher in the initial 30 minutes.
3. A better hemodynamic profile.
4. Significantly prolonged duration of post operative analgesia.
5. No incidence of pruritis.

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CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **Dr E.BALAJI,** post graduate in department of Anaesthesiology, Raja Mirasudhar Hospital attached to Thanjavur medical college & hospital, Thanjavur and to use my personal clinical data for the purpose of analysis and to compare the effect of study drugs.

Place :

Date : Signature of participant

PROFORMA

NAME: AGE: SEX: FEMALE
IP NO:

HT: WT:

DIAGNOSIS:

SURGERY: SURGERY DURATION:

ASA Physical Status:

Co-Morbidity:

Any drugs:

GROUP	**A**	**B**

REGIONAL ANAESTHESIA/ SUB ARACHANOID BLOCK

Level:

Parameters

Pre- OP:

PR: SBP: DBP: MAP:
SPO2:

MOTOR BLOCKADE (MODIFIED BROMAGE SCORE)

MOTOR LEVEL	0	1	2	3
TIME				

MODIFIED BROMAGE SCORE

Grade	**Criteria**	**Degree of block**
0	Able to move hip, knee, ankle.	Nil (0%)
1	Unable to move hip, but able move knee and ankle.	Partial (33%)
2	Unable to move hip and knee, but able to move ankle.	Almost complete (66%)
3	Unable to move hip, knee and ankle.	Complete (100%)

Time of onset:

Time for maximum motor blockade:

SENSORY BLOCKADE (COLD TOUCH)

SENSORY LEVEL	FOR T6	MAXIMUM BLOCK	Two segment regression time
TIME			

Time of onset:

Time for maximum sensory blockade/maximum sensory level:

Two segment regression time:

SEDATION SCORE (RAMSAY SEDATION SCORE)

TIME	½ hr	IInd ½ hr	2HRS	4HRS	6HRS
SEDATION SCORE					

RAMSAY SEDATION SCORE:

1 → Patient is anxious and agitated or restless, or both

2 → Patient is cooperative, oriented and tranquil

3 → Patient responds to commands only

4 → Patient exhibits brisk response to light glabellar tap or loud auditory stimulus

5 → Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus

6 → Patient exhibits no response

HAEMODYNAMICS:

TIME	PR	SBP	DBP	MAP	SP02
0MIN					
3MIN					
6MIN					
9MIN					
12MIN					
15MIN					
30MIN					
60MIN					

INTRA-OP Inj.Ephedrine Inj.Atropine
Inj.oxyctocin

Any other Drugs

ANALGESIA = Inj. Tramadol 100 mg intra muscular at end of 45 mins from SAB

COMPLICATIONS:

COMPLICATIONS	GROUP A	GROUP B
Nausea		
Vomiting		
Pruritis		
Others		

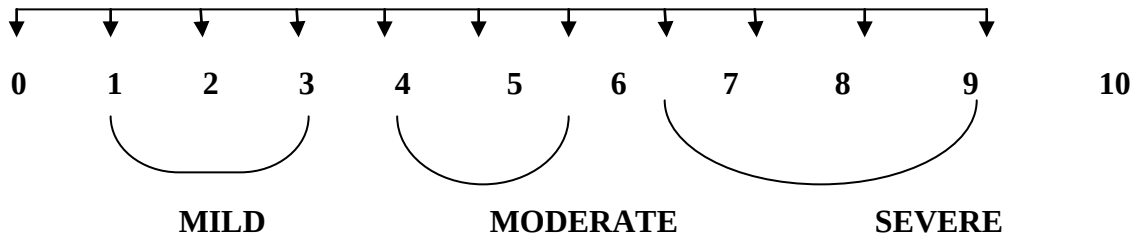
APGAR SCORE:

	0	1	2	1MIN	5MIN
COLOUR	Blue/pale	Pink body/Blue extremities	Completely pink		
HR	Absent	Slow(<100/min)	Regular(>100/min)		
RESPIRATORY EFFORT	Absent	Slow, Irregular	Good, crying		
TONE	Limp	Some flexion	Active motion		
REFLEX IRRITABILITY	No response	Grimace	Cough,sneeze,cry		
TOTAL					

POST-OP PAIN SCORE (VAS SCORE)

TIME	60 min	90 min	105 min	120 min	150 min	180 min	210 min	240 min	270 min	300 min	360 min
SCORE											

VAS SCORE



TIME FOR FIRST REQUEST FOR ANALGESIA:

Thanjavur Medical College

THANJAVUR, TAMILNADU, INDIA - 613001

(Affiliated to the T.N.Dr.MGR Medical University, Chennai)

INSTITUTIONAL ETHICAL COMMITTEE

CERTIFICATE

Approval No. : 136

This is to certify that The Research Proposal / Project titled

.....RANDOMIZED DOUBLE BLINDED COMPARATIVE STUDY OF.....

ADDING DEXMEDETOMIDINE VERSUS FENTANYL WITH BUPIVACAINE IN... SPINAL ANAESTHESIA FOR UNCOMPLICATED CAESAREAN SECTION.

submitted by Dr. .....E. BALAJI..... **of**

Dept. of .....ANAESTHESIOLOGY..... **Thanjavur Medical College, Thanjavur**

was approved by the Ethical Committee.

Thanjavur

Dated : ...10.04.2015...

THANJAVUR MEDICAL COLLEGE M.E UNIT THANJAVUR-4

Secretary
Ethical Committee
TMC, Thanjavur.

THE SECRETARY
INSTITUTIONAL ETHICAL COMMITTEE
THANJAVUR MEDICAL COLLEGE,
THANJAVUR.

KEY TO ABBREVATIONS

IM = intra muscular

IV = intra venous

PACU = post anaesthetic care unit

LSCS = lower segment caesarean section

NIBP = non invasive blood pressure

SPO2 = oxygen saturation

mm of Hg = millimeters of mercury

cms = centimeters

kgs = kilograms

mg = milligram

µgm = microgram

ml = milliliter

ASA = American society of anaesthesiology classification

GROUP-A

S.NO	NAME	AGE	HEIGHT	WEIGHT	PREV.LSCS	ASA	DURATION OF SURGERY(MIN)	PREOPERATIVE HEMODYNAMICS				MOTOR BLOCK TIME(MIN)	
								PR	SBP	DBP	MAP	SPO2	ONSET	COMPLETE
1	GEETHAPRIYA	30	150	70	YES	II	40	102	128	78	88	100	2	4
2	MARY PRINCY	23	159	69	YES	II	40	86	130	77	91	99	1	2
3	RAMANI	29	146	60	YES	II	40	90	122	76	86	99	1	3
4	JEYAM	26	145	52	YES	II	40	72	121	67	84	99	1	3
5	KALAISELVI	27	148	50	YES	II	45	86	100	60	72	100	1	3
6	NARMADHA	27	162	65	NO	II	40	104	148	82	100	99	2	4
7	INICKAO	21	141	46	YES	II	40	106	132	98	108	99	1	4
8	PUSHPA	21	152	55	NO	II	45	110	136	80	96	99	2	6
9	RAJAMANI	29	146	60	YES	II	45	90	122	76	86	99	2	6
10	GEETHA	26	146	48	YES	II	60	96	126	78	92	99	2	6
11	SUBHASINI(EL)	25	144	60	YES	II	45	88	132	88	96	99	2	5
12	JHANSI	34	144	60	YES	II	60	84	126	78	88	99	2	5
13	ANITHA	21	152	66	NO	II	60	86	136	80	92	99	2	4
14	SHEELA(EL)	35	151	65	NO	II	50	70	140	86	100	99	1	5
15	SATHYA	21	150	52	NO	II	45	104	130	80	96	99	1	3
16	RAJESHWARI	22	156	56	NO	II	50	96	136	84	96	99	2	4
17	ALPHONSA	26	154	70	NO	II	45	96	136	82	94	99	3	6
18	JEEVA	32	148	52	YES	II	70	88	132	80	92	99	2	4
19	RAZIYA	26	146	50	YES	II	60	84	132	84	96	99	2	5
20	CHITRADEVI	22	144	50	NO	II	45	104	126	82	94	99	3	9
21	REGIMA	26	152	56	YES	II	75	92	136	86	98	99	2	7
22	SHANTHI	24	154	60	NO	II	60	88	136	80	96	99	4	6
23	PUSHPA	21	150	55	YES	II	45	110	134	84	94	99	1	4
24	ARULARASI	30	147	45	YES	II	60	96	136	82	96	99	3	9
25	SHARMILA	24	146	48	NO	II	45	78	122	76	86	99	4	9
26	MANIMEGALAI	27	140	45	NO	II	60	90	140	76	88	99	3	8
27	JEEVITHA	30	146	50	NO	II	45	84	130	80	94	99	3	7
28	SEEETHA	27	150	56	YES	II	60	90	140	86	98	99	3	6
29	REVATHY	25	152	50	NO	II	45	84	138	82	96	99	3	8
30	JAYA	24	145	52	YES	II	40	72	120	67	83	99	1	3

SENSORY BLOCK TIME(MIN)			2 SEG REG TIME(MIN)					PULSE RATE(MIN)								SYSTOLIC BLOO			
ONSET(T6)	MAX BLOCK LEVEL	TIME(MIN)		first ½hr	second½hr	2HR	6HR	OMIN	3MIN	6MIN	9MIN	12MIN	15MIN	30MIN	60 MIN	0MIN	3MIN	6MIN	9MIN
4	T4	15	60	2	2	2	2	108	119	105	100	98	107	116	96	108	88	119	108
3	T2	12	90	2	2	2	2	90	101	85	78	81	86	101	102	117	120	102	112
5	T4	16	75	2	2	2	2	121	124	102	96	92	88	88	76	124	105	103	104
2	T2	14	90	2	2	2	2	76	62	55	56	58	58	58	69	115	97	118	118
2	T2	9	90	2	2	2	2	108	116	136	104	96	83	90	86	96	101	86	98
5	T6	18	105	2	2	2	2	112	104	96	92	88	101	96	90	132	126	130	122
4	T4	15	110	2	2	2	2	99	96	101	102	104	108	116	106	134	120	112	116
4	T3	16	70	2	2	2	2	104	98	90	86	80	76	72	66	126	124	116	112
5	T4	16	75	2	2	2	2	121	124	102	96	90	88	88	76	124	105	103	105
3	T4	12	90	2	2	2	2	96	104	88	82	80	78	70	70	126	118	112	106
2	T2	12	90	2	2	2	2	90	86	92	88	84	80	64	65	136	124	110	106
5	T2	12	110	2	2	2	2	96	104	100	88	80	76	76	78	136	124	118	112
3	T4	10	90	2	2	2	2	86	104	96	90	80	78	82	84	136	124	112	100
4	T4	9	105	2	2	2	2	72	66	55	66	88	104	98	88	140	112	96	104
3	T3	7	90	2	2	2	2	104	96	90	80	76	70	80	78	130	120	98	102
4	T2	14	105	1	2	2	2	96	104	100	88	80	76	76	78	136	124	118	110
4	T4	9	90	1	2	2	2	96	98	102	94	88	84	80	74	130	124	118	110
4	T2	10	105	2	2	2	2	88	82	70	72	74	78	74	78	130	126	110	106
4	T3	12	105	2	2	2	2	88	86	78	74	74	72	90	78	126	112	96	102
7	T4	12	90	2	2	2	2	104	100	88	80	80	78	80	84	126	122	116	110
6	T4	10	105	2	2	2	2	96	90	80	76	70	68	70	88	136	116	109	104
6	T3	10	105	2	2	2	2	86	80	84	78	82	80	80	72	136	124	114	106
4	T3	16	70	2	2	2	2	104	98	90	86	84	84	72	66	126	124	116	114
8	T4	15	105	2	2	2	2	98	90	86	72	62	56	96	76	138	124	114	110
6	T4	15	90	2	2	2	2	96	90	86	80	76	74	86	78	136	128	124	112
6	T3	16	105	1	2	2	2	92	96	102	94	90	86	100	76	140	128	116	112
5	T4	10	95	2	2	2	2	90	82	72	70	66	64	80	70	130	122	114	108
6	T4	10	90	2	2	2	2	98	90	82	72	66	64	74	76	140	122	112	104
8	T4	15	100	2	2	2	2	86	94	90	84	78	72	80	76	138	124	116	108
2	T2	14	90	3	2	2	2	76	62	55	58	56	58	58	69	115	97	118	116

)D PRESSURE(MIN)				DIASTOLIC BLOOD PRESSURE(MIN)								MEAN ARTERIAL PRESSURE(MIN)							
12MIN	15MIN	30MIN	60MIN	0 MIN	3MIN	6MIN	9MIN	12MIN	15MIN	30MIN	60MIN	0MIN	3MIN	6MIN	9MIN	12MIN	15MIN	30MIN	60MIN	0MIN
104	119	96	120	56	40	63	60	50	52	44	66	70	54	77	70	61	68	58	78	100
116	105	111	106	71	50	51	58	54	44	54	52	82	73	63	66	69	56	67	67	100
107	90	115	114	78	62	60	58	55	52	58	60	92	75	73	70	67	61	74	74	99
120	122	120	127	76	49	56	58	60	65	70	68	88	60	70	74	78	78	78	80	99
109	101	97	106	55	57	46	50	59	51	50	58	68	70	55	60	71	63	64	70	100
127	131	110	118	74	64	62	60	60	59	48	66	86	78	78	76	72	78	66	78	100
119	115	106	116	94	81	78	76	76	71	55	71	102	87	87	85	84	81	67	81	99
110	104	94	104	80	78	70	68	66	64	54	60	92	90	86	82	80	78	64	74	100
107	90	115	114	78	62	60	58	56	52	58	60	92	75	73	70	67	60	74	74	99
102	96	92	106	78	76	72	66	62	56	52	62	90	88	86	78	74	68	56	70	99
104	90	92	110	88	76	70	68	62	56	56	66	98	88	84	78	70	64	64	76	99
108	106	96	118	84	78	72	66	64	64	54	68	96	88	82	78	74	74	64	88	99
94	112	96	108	80	72	68	62	52	66	52	72	92	84	80	70	62	78	62	84	99
106	104	94	112	86	66	52	58	60	60	60	68	100	76	62	66	72	72	72	78	99
106	104	92	108	80	72	52	56	66	64	56	64	96	82	64	68	76	74	66	74	99
108	108	96	118	84	78	72	66	64	64	54	68	96	88	82	78	74	74	64	80	99
108	106	94	118	82	78	72	68	66	64	54	66	94	88	84	80	76	74	66	76	99
96	116	108	116	82	76	66	62	54	72	64	72	94	88	76	70	64	84	74	84	99
118	94	112	116	80	66	52	60	74	56	64	66	92	76	62	70	86	66	74	78	99
102	92	94	108	82	78	72	66	60	50	52	66	94	90	84	78	72	60	64	74	99
96	112	96	106	86	66	64	60	56	62	54	62	98	78	76	70	65	74	66	70	99
96	122	114	110	86	76	74	66	54	74	64	64	98	86	84	76	64	86	74	74	99
110	104	94	104	80	78	70	68	66	64	54	60	92	90	86	84	80	78	64	74	100
106	120	116	108	80	80	72	66	56	66	66	60	92	90	82	74	66	76	76	70	99
106	96	118	108	76	74	70	68	62	54	74	66	88	84	82	66	72	66	84	76	99
110	98	118	112	76	70	66	66	64	62	70	64	88	82	76	72	74	72	80	74	99
104	106	112	110	80	76	64	60	56	60	66	72	94	90	76	70	66	70	76	84	99
96	94	118	110	86	76	70	62	54	52	66	62	98	90	84	76	66	62	76	72	99
102	98	120	114	82	72	66	62	60	54	66	66	94	84	78	74	70	66	74	76	99
120	122	120	127	76	48	56	58	60	64	70	68	89	58	70	74	78	78	79	80	99

SPO2			EPHEDRINE REQ	EPHEDRINE (mg)	ATROPINE REQ	COMPLICATIONS				APGAR		TIME FOR RESCUE ANALGESIA(MINS)
15MIN	30MIN	60MIN				NAUSEA	VOMITING	PRURITIS	OTHERS	1MIN	5MINS	
99	100	100	YES	30	NO	YES	NO	NO	NO	9	10	180
100	100	98	NO	18	NO	YES	NO	NO	NO	9	10	240
100	100	99	YES	6	NO	NO	NO	NO	NO	9	9	240
100	99	100	YES	6	NO	NO	NO	NO	NO	9	9	240
100	100	100	YES	24	NO	NO	NO	NO	NO	9	9	300
100	100	100	NO	0	NO	NO	NO	NO	NO	7	9	240
99	99	99	YES	6	NO	YES	YES	NO	NO	8	9	300
100	99	99	YES	6	NO	YES	NO	NO	NO	8	9	240
100	99	100	YES	6	NO	NO	NO	NO	NO	7	9	180
99	99	99	YES	12	NO	NO	NO	NO	NO	8	10	240
99	100	99	NO	18	NO	YES	NO	NO	NO	7	9	240
99	98	99	YES	6	NO	YES	YES	NO	NO	8	9	210
99	99	99	YES	12	NO	NO	NO	NO	NO	9	10	210
99	98	99	NO	18	YES	YES	NO	NO	NO	6	9	270
98	99	99	YES	18	NO	NO	YES	NO	NO	7	9	270
99	99	99	YES	6	NO	NO	NO	NO	NO	9	10	210
99	99	99	NO	6	NO	NO	YES	NO	NO	8	9	240
99	99	99	YES	6	NO	NO	NO	NO	NO	8	9	180
99	99	99	NO	9	NO	YES	YES	NO	NO	9	10	240
99	99	99	YES	18	NO	YES	NO	NO	NO	7	10	240
99	99	99	YES	12	NO	YES	YES	NO	NO	8	10	210
99	99	99	YES	6	NO	YES	NO	NO	NO	9	10	240
100	100	100	YES	6	NO	YES	NO	NO	NO	9	10	240
99	99	99	NO	0	YES	NO	NO	NO	NO	6	9	210
99	99	99	YES	9	NO	YES	NO	NO	NO	8	10	210
99	99	99	YES	3	NO	YES	NO	NO	NO	7	9	240
99	97	99	NO	0	NO	NO	NO	NO	NO	6	9	210
98	99	99	YES	6	NO	NO	NO	NO	NO	8	10	240
99	99	99	YES	6	NO	YES	NO	NO	NO	7	9	210
97	99	99	YES	6	NO	NO	NO	NO	NO	9	9	240

GROUP-B

S.NO	NAME	AGE	HEIGHT	WEIGHT	PREV.LSCS	ASA	DURATION	PREOPERATIVE HEMODYNAMICS					MOTOR BLOCK TIME(MIN)	
								PR	SBP	DBP	MAP	SPO2	ONSET	COMPLETE
1	VASANTHA	32	154	60	YES	II	60	90	140	90	102	99	3	8
2	ANJALAI	26	148	52	NO	II	40	86	124	74	86	99	4	8
3	JEENATH	26	160	75	YES	II	60	90	140	86	98	99	3	6
4	ANUSHYA	24	143	50	NO	II	40	88	124	72	84	99	2	6
5	RAJI	32	160	67	YES	II	60	78	130	80	92	99	3	6
6	JENIFER	26	156	60	NO	II	50	76	130	80	92	99	3	6
7	PUSHPALATHA	24	146	46	NO	II	40	96	136	76	88	99	4	10
8	SOUNDARI	27	148	56	NO	II	40	96	140	80	96	99	3	6
9	JHANSI	28	156	62	YES	II	50	86	130	82	92	99	3	8
10	DHANALAKSHMI	26	152	56	NO	II	60	96	130	80	92	99	4	6
11	SUSAN	22	152	68	NO	II	60	102	140	86	98	99	4	6
12	POORNIMA	26	152	50	YES	II	60	98	130	80	92	99	2	6
13	FATHIMA	26	154	54	YES	II	60	96	126	80	92	99	2	6
14	KARTHIGA	26	149	54	YES	II	60	90	126	76	84	99	4	7
15	SEETHALAKSHMI	27	148	54	YES	II	60	90	126	76	88	99	3	6
16	RAJESHWARI	21	146	51	NO	II	45	98	130	80	96	98	4	6
17	MAHESHWARI	22	142	48	NO	II	45	104	132	86	98	99	2	8
18	VIDHYA	26	150	52	NO	II	50	90	126	80	96	99	1	4
19	VAITHESSWARI	26	144	50	YES	II	50	106	136	86	98	99	2	5
20	RAMYA	32	162	68	YES	II	60	90	136	84	94	99	3	7
21	SUDHA	24	146	52	NO	II	45	96	126	74	86	99	2	4
22	SHAKILA	26	152	46	NO	II	45	94	130	80	94	99	3	6
23	SELVI	32	152	60	YES	II	60	94	136	80	96	99	1	3
24	SATHYA	22	148	60	YES	II	50	76	130	78	90	99	2	6
25	RENUKA	21	148	66	NO	II	40	98	140	86	100	99	1	3
26	RADHA	26	144	50	YES	II	50	106	136	86	98	99	2	5
27	SINDHU	34	156	65	NO	II	45	78	136	86	98	99	1	5
28	Ranjitha	22	142	48	NO	II	45	104	132	86	98	99	2	8
29	KUMDHA	28	148	50	YES	II	60	90	126	80	94	99	2	6
30	SANGEETHA	28	160	75	NO	II	60	86	146	86	100	99	2	6

SENSORY BLOCK TIME(MIN)			2 SEG REG TIME(MIN)					PULSE RATE(MIN)							
ONSET(T6)	MAX BLOCK LEVEL	TIME(MIN)		first ½hr	second ½hı	2HR	6HR	OMIN	3MIN	6MIN	9MIN	12MIN	15MIN	30MIN	60 MIN
6	T4	16	90	2	2	2	2	90	78	74	72	66	54	90	78
6	T2	15	90	2	2	2	2	86	94	90	86	76	66	80	84
8	T4	16	90	2	2	2	2	98	90	84	82	78	72	84	80
6	T2	10	75	2	2	2	2	88	86	76	74	94	84	86	86
5	T3	15	90	2	2	2	2	78	86	84	78	72	66	86	80
6	T4	16	70	2	2	2	2	76	74	70	68	66	56	84	74
6	T4	15	60	2	2	2	2	90	94	80	76	74	66	74	66
4	T4	15	90	2	2	2	2	98	96	90	86	80	96	80	74
5	T3	15	90	2	2	2	2	108	88	84	82	104	80	82	74
4	T2	15	90	2	2	2	2	108	94	88	80	72	96	94	88
6	T3	12	90	2	2	2	2	106	92	98	88	64	60	98	82
2	T4	8	90	2	3	2	2	98	94	52	60	88	104	82	84
2	T4	12	90	2	2	2	2	98	94	84	72	66	104	82	84
5	T3	13	90	2	2	2	2	90	84	66	64	66	96	80	72
5	T2	14	105	2	2	2	2	90	84	66	64	66	90	78	74
6	T2	14	90	2	2	2	2	98	76	74	68	66	78	98	90
4	T4	10	90	2	3	2	2	106	76	62	66	68	90	80	78
3	T4	8	90	1	2	2	2	96	90	84	84	80	66	66	74
4	T3	10	105	2	2	2	2	106	96	80	70	64	66	70	72
6	T3	15	90	2	2	2	2	96	88	84	78	74	90	84	76
6	T2	14	105	2	2	2	2	96	90	84	88	78	100	80	70
4	T4	15	90	2	2	2	2	96	94	88	84	82	74	78	74
3	T2	6	90	2	2	2	2	98	90	76	66	64	68	74	72
3	T4	9	75	2	2	2	2	78	74	66	66	64	52	90	78
4	T3	12	75	2	2	2	2	98	106	96	84	80	74	90	80
4	T3	10	105	2	2	2	2	106	96	80	68	66	66	70	72
4	T4	8	90	2	2	2	2	78	74	64	66	80	94	62	66
4	T4	10	90	2	2	2	2	106	76	62	78	98	90	80	78
6	T4	12	75	2	2	2	2	96	84	74	64	66	66	86	90
3	T4	12	90	2	2	2	2	86	80	78	72	66	80	76	72

SYSTOLIC BLOOD PRESSURE(MIN)								DIASTOLIC BLOOD PRESSURE(MIN)							
0MIN	3MIN	6MIN	9MIN	12MIN	15MIN	30MIN	60MIN	0 MIN	3MIN	6MIN	9MIN	12MIN	15MIN	30MIN	60MIN	0MIN
140	130	122	114	110	110	94	110	90	84	72	72	72	70	54	60	102
130	122	114	110	104	90	96	114	72	70	64	62	56	48	52	72	84
140	122	120	114	104	96	118	112	86	78	76	72	66	56	70	64	98
124	114	94	98	108	96	94	106	72	66	54	56	66	56	54	68	84
130	122	114	104	100	94	118	108	80	72	62	62	60	54	70	64	92
136	106	92	122	118	114	94	110	80	64	56	78	76	74	50	70	92
126	106	94	118	116	110	96	110	70	64	58	72	70	66	58	70	82
140	122	114	104	94	122	114	108	80	72	66	62	54	72	66	60	96
136	122	116	102	94	108	96	120	86	72	66	54	52	64	56	74	98
130	124	106	96	94	116	94	118	82	74	66	52	52	66	56	72	96
140	122	106	94	96	94	108	112	86	72	62	54	56	50	60	66	98
130	126	112	96	94	106	92	112	80	74	66	54	54	62	48	72	94
136	126	112	96	94	104	92	112	80	74	66	60	54	66	48	72	94
126	116	110	104	94	120	96	110	82	70	68	62	50	76	56	68	94
126	118	110	104	94	122	96	110	82	72	68	62	52	78	56	68	94
130	122	116	106	94	110	92	106	86	80	72	66	52	68	50	72	98
132	108	96	94	120	112	92	114	84	66	54	64	78	66	50	66	96
126	112	106	102	94	102	96	114	80	72	66	62	49	56	52	74	96
136	126	122	112	110	104	92	118	86	78	74	66	62	58	48	68	98
136	124	118	104	94	122	114	108	86	78	66	60	54	76	66	60	96
126	114	108	102	94	118	96	108	76	70	66	62	52	72	56	66	86
130	118	108	106	94	122	116	110	86	74	66	64	54	76	68	66	96
136	122	112	106	94	112	104	112	80	66	66	56	46	66	60	72	96
130	112	94	104	112	110	96	110	78	66	50	66	72	70	54	66	90
140	126	112	108	108	102	90	120	86	76	70	66	64	60	48	72	98
136	126	122	112	110	104	92	118	86	78	74	66	62	58	48	68	98
136	120	106	96	96	118	94	16	86	66	58	50	48	66	50	76	98
132	104	96	96	120	112	92	114	84	66	54	54	78	66	50	66	96
136	112	104	96	94	112	96	108	86	62	60	52	48	66	52	64	100
136	122	118	110	96	118	94	108	86	78	72	58	54	72	52	64	96

MEAN ARTERIAL PRESSURE(MIN)							SPO2			EPHEDRINE REQ	EPHEDRINE (mg)	ATROPINE REQ	
3MIN	6MIN	9MIN	12MIN	15MIN	30MIN	60MIN	0MIN	15MIN	30MIN	60MIN				NAUSEA
94	84	84	84	82	66	66	99	99	99	99	YES	6	YES	NO
82	74	70	66	58	62	84	99	99	99	99	YES	12	NO	NO
90	88	82	76	66	82	74	99	99	98	99	NO	6	NO	NO
76	64	66	76	66	64	78	99	99	99	99	YES	15	NO	YES
84	74	74	70	64	76	74	99	99	99	99	YES	6	NO	YES
74	66	90	88	84	60	82	99	98	99	99	YES	12	YES	YES
74	68	82	80	76	70	82	99	99	99	99	YES	12	NO	YES
82	76	70	66	84	74	70	99	99	98	99	YES	6	NO	NO
84	76	66	62	76	66	76	99	99	99	99	NO	9	NO	YES
84	74	62	62	76	66	84	99	99	99	99	YES	12	NO	NO
84	74	64	68	62	74	76	99	99	96	99	YES	24	NO	NO
84	76	64	62	70	58	84	99	99	99	99	NO	18	YES	YES
84	76	64	62	62	58	84	99	99	99	99	YES	18	NO	NO
82	76	70	62	88	66	76	99	99	99	99	YES	12	NO	NO
82	76	72	62	88	66	76	99	99	96	99	YES	12	NO	YES
92	84	74	64	78	64	82	99	99	99	99	YES	12	NO	YES
74	64	76	88	76	60	76	99	99	99	99	YES	18	NO	NO
88	80	76	64	66	62	84	99	99	98	99	YES	12	NO	YES
88	86	78	72	66	60	72	99	99	99	99	NO	12	NO	YES
88	76	70	64	88	76	70	99	99	99	99	YES	6	NO	YES
82	76	72	62	84	66	76	99	99	99	99	YES	12	NO	YES
84	76	74	64	86	76	76	99	99	99	99	NO	6	NO	NO
78	76	68	58	78	74	82	99	99	99	99	YES	12	NO	NO
78	60	76	70	80	64	74	99	99	99	99	YES	12	YES	YES
88	82	72	70	66	58	82	99	99	99	99	NO	6	NO	NO
88	86	84	72	66	60	78	99	99	99	99	YES	12	NO	YES
76	68	60	58	82	60	88	99	99	99	99	NO	12	NO	NO
74	64	64	88	76	60	76	99	99	99	99	YES	18	NO	NO
74	72	66	84	78	64	76	99	99	99	99	NO	12	NO	NO
88	82	76	64	82	62	74	99	99	99	99	YES	12	NO	NO

COMPLICATIONS			APGAR		TIME FOR RESCUE ANALGESIA(MINS)
VOMITING	PRURITIS	OTHERS	1MIN	5MINS	
NO	YES	NO	8	10	150
NO	YES	NO	8	9	150
NO	YES	NO	8	10	120
YES	NO	NO	8	10	150
NO	YES	NO	8	9	120
NO	NO	NO	9	10	135
NO	YES	NO	8	10	120
NO	YES	NO	8	10	120
NO	NO	NO	9	10	150
YES	NO	NO	8	10	150
NO	NO	NO	9	10	150
NO	YES	NO	7	10	120
NO	YES	NO	7	10	150
YES	NO	NO	7	10	150
YES	YES	NO	7	10	150
NO	NO	NO	8	10	150
NO	YES	NO	8	10	150
NO	YES	NO	9	10	150
YES	YES	NO	7	10	180
NO	YES	NO	8	9	180
NO	NO	NO	8	10	180
NO	YES	NO	9	10	180
NO	YES	NO	8	10	180
NO	YES	NO	7	10	150
YES	NO	NO	7	10	150
YES	YES	NO	7	10	180
YES	YES	NO	8	10	180
NO	YES	NO	8	10	150
NO	NO	NO	7	10	150
NO	YES	NO	7	9	150